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THE CHICAGO MEDICAL SCHOOL
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VOLUME 19 NOVEMBER 1958 NUMBER 4

SOME BIOLOGICAL CONSIDERATIONS IN AMEBIASIS

JAMES G. SHAFFER, Ph.D.* and WILLIAM H. SHLAES, M.D.**

The association of *Entamoeba histolytica* with acute fulminating amebic dysentery and with such complications as liver, lung and brain abscess and cutaneous amebiasis has long been recognized (Rees, 1955). There would seem to be no question about the primary role of the amebas in such situations; but the mechanism by which the ameba manages to produce these conditions is not well understood. It has also been known for many years that a considerable percent of individuals infected with *E. histolytica* do not develop acute dysentery. In some instances the infected individual may never reveal symptoms referrable to the amebic infection; in others there may develop a chronic disease which has an irregular course covering many months which varies from periods of good health to acute exacerbations of gastro-intestinal disease presenting definite diagnostic problems. These latter cases may be called "chronic amebiasis" to distinguish them from acute amebic dysentery.

It is of interest to speculate on the possible reasons for the great differences in the outcome of infection with *E. hystolytica*.

The first possibility that presents itself is variation in the pathogenic potential of different strains of *E. histolytica*. A number of workers have presented evidence (Meleney and Frye, 1937; Hunninen and Boone, 1957, etc.) from animal experimentation indicating such differences. Meleney and Frye found that strains of *E. histolytica* obtained from patients infected during the famous Chicago World's Fair outbreak and from an outbreak in Tennessee were more pathogenic for kittens than were strains isolated from persons living in an area where a high percent of the population was infected, but where there was no acute dystentery. Hunninen and Boone showed some correlation between the pathogenicity of strains of *E. histolytica* for humans and rabbits. Thus, there is definite evidence of variation amongst strains. This is probably an important factor, but that this is not the only determining point is indicated by other evidence.

Elsdon-Dew, et. al. (1946), in studies of *E. histolytica* infections in South Africa have reported that the various racial groups in that area are affected quite differently. Among the Bantus, the disease is acute and fulminating, while in the whites and the Indian population the most common thing is chronic amebiasis. This is even true in areas where these groups live in relatively close proximity, although the living conditions vary. Since one might suspect that all are exposed to the same amebas, the explanation of these difference in response must lie in other points. It could be postulated quite reasonably that these observations indicate racial differences in susceptibility to the disease. It would not be sur-

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prising to find such a situation here, since such racial differences in susceptibility exist in other diseases. But before it is finally decided how much race is involved, it will be necessary to investigate other factors. The dietary habits of the Bantu are somewhat different than the other races and this may be of considerable importance.

That diet is indeed very important is indicated by the studies of Taylor, et. al. (1952), Faust, et. al. (1934), Jones (1946), and others who have shown that the number of successful infections in guinea pigs and certain other laboratory animals, accomplished by intracaecal inoculation, can be changed by modifying the diet of the animals. Alexander and Meleney (1953) studied the diets of persons in two different communities in Tennessee. In both communities there was a high incidence of amebic infection, but in one community with a better diet there was considerably lower incidence of dysentery than there was in the other community.

Hints as to other determining factors can be obtained by observation of individuals with chronic amebiasis. Acute exacerbations of diarrhea and other symptoms often occur in these individuals during periods of stress or fatigue, or following the ingestion of certain foods or alcoholic beverages. It is simple to say that stress and dietary factors have changed the susceptibility of the host, but when one attempts to ascertain what the mechanism of these changes is, the situation becomes very complex. Diet can probably change the bacterial flora in the intestine and it could be postulated that such changes might occur rather rapidly. The combination of food and/or drink that may be irritating to the intestinal epithelium and also cause significant changes in the intestinal flora could easily influence the uneasy host-parasite balance and result in disease. It is possible that stress can do the same things as diet insofar as its influence on the intestine is concerned.

That the bacterial flora or intestinal content is of importance in the pathogenesis of amebiasis has been indicated for some time. Findings have indicated that experimental infections in animals were difficult to accomplish with amebas from the relatively bacteria-free Shaffer-Frye medium (Balsam and Shaffer, 1958) or the trypanosome medium of Phillips (Phillips and Bartgis, 1954; Luttermoser and Phillips, 1952). Further confirmation is to be found in the recent findings of Phillips, et. al. (1958) with germ-free guinea pigs in which the addition of stool filtrate to trypanosome grown amebas resulted in disease, where none occurred without the filtrate. Thus, there seems little doubt that the environment in which *E. histolytica* exists exerts a great deal of influence on its functional ability.

One can then perhaps render a pathogenic strain a nonpathogen merely by changing its environment and this might well take place right within the intestine of the infected individual. Thus, in a given amebic infection, the amebas might change back and forth between the pathogenic and non-pathogenic state as a result of fluctuations in the conditions of the gut. Westphal, (1937) after infecting himself with *E. histolytica*, carried the organism for several months. He then swallowed the bacterial flora from a case of amebiasis and promptly developed acute amebic dysentery. Perhaps this is a case where the amebas were changed by their environment.

Some evidence for the influence of environment on the ability of cells to function may be derived from work done in tissue culture, where although cells may grow and multiply quite well, they fail to react to treatment with hormones and certain other agents capable of producing marked effects on cells *in vivo*. One explanation for this failure is that, although conditions are adequate for growth and multiplication in the tissue culture, the environment is not proper for the cells to be completely functional. Perhaps a similar situation exists with *E. histolytica*, that is, it requires certain elements in its environment to become functional to the extent of being able to invade tissue in the host.

To summarize at this point, it seems likely that the outcome and course of infection with *E. histolytica* depends on

many factors involving both host and parasite. Not only may a certain factor influence either the host or the parasite, but may influence both at the same time. The situation is one of constant change and with the information available at present, there is no way of predicting the course of events. Thus, whenever *E. histolytica* is found in the stool of an individual, it must be viewed with the realization that, although the infected individual may not at the moment be suffering any ill effects, the conditions may change at any time to one from which the disease may result.

There is yet another complication in amebiasis. It has been recognized for a number of years that great variation in size exists in the organisms classified as *Entamoeba histolytica* and it is now fairly well established that at least two races exist. The small race includes all morphologically typical *E. histolytica* with cyst sizes below 10 microns and the large race has cysts over 10 microns in diameter. In Figure 1 are shown photomicrographs of cysts and trophozoites of small and large race *E. histolytica.*

There has been much speculation on the relationship between small and large race *E. histolytica,* but little definitive work has been done since few successful isolations of small race amebas have been made into culture. A number of workers (Felsenfeld and Young, 1945; Sapero, et. al., 1942) have commented on the difficulties of culturing small race strains. Recently, McQuay (1956) has described a medium in which the small race can be cultured from the stools of infected individuals and can be established in mixed bacterial flora through serial transplants. A number of strains have been obtained from McQuay and certain comparisons between these and the large race strains have been made by the authors.

The results of observations to date indicate that there is considerable fundamental difference between the races. First, there are obvious differences in the cultural requirements of the two races. The failure of small race *E. histolytica* to grow on first isolation in media capable of supporting excellent growth of the large race as observed by the authors and others is certainly indicative. Further, it has not been possible to establish any of the small race strains in the Shaffer-Frye medium (Shaffer, et. al., 1949) in which large race strains grow very well. Thus, their metabolic requirements are perhaps different. Second, it has been found that penicillin exerts effects on the small race that it does not exhibit with the large race (Shaffer, et. al., 1957). Third, the small race does not ingest red blood cells, a very well known diagnostic characteristic of the large race. Fourth, it has been observed that the small race cyst tends to be 2-nucleate rather than 4-nucleate as is the case with the large race (Shaffer, et. al., 1958).

Thus, there is a growing body of evidence suggesting that the small race *E. histolytica* is a separate entity and it may be necessary to re-classify these organisms in due time. It has been suggested that the small race *E. histolytica* may represent less pathogenic mutants derived from large race strains in the infected individual during the time between an initial infection and the development of chronic amebiasis. Since, in this laboratory, there has been no tendency of the amebas to undergo changes measurable by the methods at hand, our feeling at this time is that such mutations are unlikely. Recently, Burrows (1957) has suggested on the basis of morphologic studies that the small forms are of at least two types, a small race *Entamoeba histolytica* and another morphologic type for which he suggests the name, *Entamoeba hartmanni.* These are very interesting observations which require further investigations of other than morphologic nature.

The incidence of infection with small race *E. histolytica* in the general population is unknown. It is to be expected that due to the difficulties in finding and identifying this organism, many infections are missed. In surveys of the findings in two laboratories in the Chicago area, it has been found that of close to 650 cases of amebiasis diagnosed at the parasitology laboratory of the Hektoen Institute of the Cook County Hospital

over a four year period, 57% were small race and in a private laboratory doing stool examinations primarily on patients with chronic gastrointestinal disease, 85% of the cases of amebiasis were small race (Shaffer, et. al., 1958). These findings do not give any clue as to the incidence of such infection in the general population, but do present evidence that this is an important human parasite and should be actively studied.

The pathogenic potential of the small race *E. histolytica* has also been the subject of much discussion. Felsenfeld (1945), pointed out that small race amebas tend to be associated with the milder forms of chronic gastro-intestinal disease. So far, no reports of extra-intestinal involvement such as liver or brain abscess have been made.

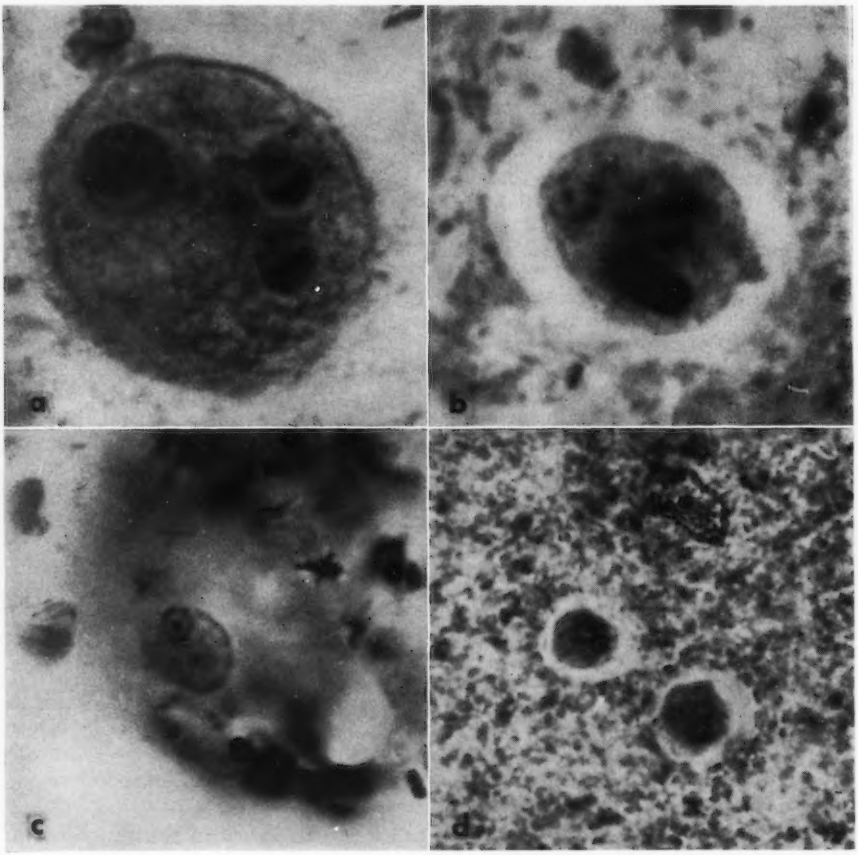

Figure 1.

Stained cysts and trophozoites of large and small race *E. histolytica* from stool specimens submitted for routine diagnosis. (a) Large race trophozoite with ingested red blood cells. The nucleus exhibits a frequently seen area of more deeply staining material. (b) Large race cyst with chromatoid bars. Note that the nucleus has an atypical arrangement of chromatin around the nuclear wall. (c) Small race trophozoite with classic nuclear structure of *E. histolytica*, with a central, compact karyosome and an evenly distributed chromatin ring. (d) Small race cysts each with 2 nuclei. Note that these cysts are very little larger than the red blood cells in (a). Modified Mallory's Phosphotungstic acid stain X approximately 2,000.

Since most of the evidence for pathogenesis of small race *E. histolytica* now resides in clinical and parasitologic findings, this discussion will be left for another presentation. Briefly, it can be said that the determination of what role, if any, is being played by these small amebas in the case of chronic GI disease in which it is frequently found will not be easy. Much further careful study will be necessary.

In view of the differences that exist between small and large race *E. histolytica* which have already been mentioned, it will not be surprising to find fundamental differences in the epidemiology and clinical manifestations of the two infections. Since the infection occurs in the complex biological system of the intestine, there will probably be much overlapping of the manifestations, making the solution of the problems quite difficult.

Further study of the fundamental nature of both small and large race *E. histolytica* is also needed. These studies must be correlated with careful clinical and parasitologic studies on patients. Amebiasis is a very interesting and, it is to be suspected, a more important disease than has been realized.

Summary

1. The outcome and course of amebic infection is dependent on a complex biological system involving both host and parasite.
2. With the present state of knowledge amebic infection in an individual must be viewed with combined suspicion and restraint.
3. Much more open-minded investigation will be necessary before the final answers to the role of *E. histolytica* and its close relatives in chronic gastro-intestinal disease is known.
4. Much further clinical and parasitologic investigation of the small race *E. histolytica* will be necessary to place it in its proper perspective.

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SOME CLINICAL CONSIDERATIONS IN AMEBIASIS

WILLIAM H. SHLAES, M.D.* and JAMES G. SHAFFER, Ph.D.**

Amebiasis, as seen in tropical and particularly in temperate zones, has been the subject for much discussion and considerable disagreement and misunderstanding for many years. Some of the reasons for this lie in the complex biology of *Entamoeba histolytica,* the complexity of which is mediated by the area of its habitat in the human host (Shaffer and Shlaes. (1958.) It is further confused by the existence of morphologically similar organisms designated now as large race *E. histolytica,* small race *E. Histolytica* and *E. hartmanni* whose interrelationships are not yet understood (Shaffer et al., 1958).

Clinically, especially in temperate zones, the situation is further confused. *E. histolytica,* when found, frequently occurs in patients with chronic symptoms referrable to the gastrointestinal tract, an area in which many agents or conditions, both known and unknown, may be responsible for part or all of the patient's presenting symptoms or findings on examination. The organism is also found in individuals who are asymptomatic.

The picture is not one that lends itself to statistical analysis at the moment, nor does it appear likely that profit would result from the collection of data on numbers of patients with this set of symptoms or that set of symptoms. The authors have attempted this on patients numbering in the hundreds, but the results have invariably been disappointing. Jones et al. (1955) working under fairly well controlled circumstances have presented rather suggestive findings.

The points to be mentioned in this article represent observations made a sufficient number of times and documented with enough care to remove them from the realm of fantasy. The purpose is to present some of the many and confusing problems faced by the physician in attempting to arrive at a reasonable diagnosis and evaluate, if possible, the role of *E. histolytica* when present in a given situation.

The term *"amebiasis"* as used in this discussion denotes merely infection with *E. histolytica* and does not necessarily imply disease. Disease may or may not be present and, when present, may or may not be the consequence of the presence of these amebas. The decision as to the importance of the parasite in any given case is a clinical one, since there are, as yet, no specific laboratory procedures available beyond the demonstration of the organism by the medical parasitologist.

More specifically, the clinical picture most frequently seen in the temperate zones is one of low grade gastro-intestinal symptoms, including, bloating after meals, selective dyspepsia to fried and fatty foods, milk and ice cream, constipation with infrequent short bursts of mild diarrhea without blood and some mild fatigue. Not infrequently, gnawing persistent hunger pain accompanied by tremulousness, relieved by food, also occurs. In our experience, when *E. histolytica* is found in patients with these symptoms, they are most commonly of the small race (Shaffer, et al., 1958). Miller (1958) found a high percent (over 50%) of small race in an office practice.

The symptoms enumerated above are easily recognized as those of, "The Irritable Colon Syndrome," and indeed, many patients with amebiasis may be diagnosed and treated for years as though they were suffering from an irritable colon. It is thought quite likely that patients harboring *E. histolytica* in their gastro-intestinal tracts actually have an "irritable colon" due to the presence of the parasite. Others may have irritable colons resulting from causes other than amebas, even though the amebas are unquestionably present. For

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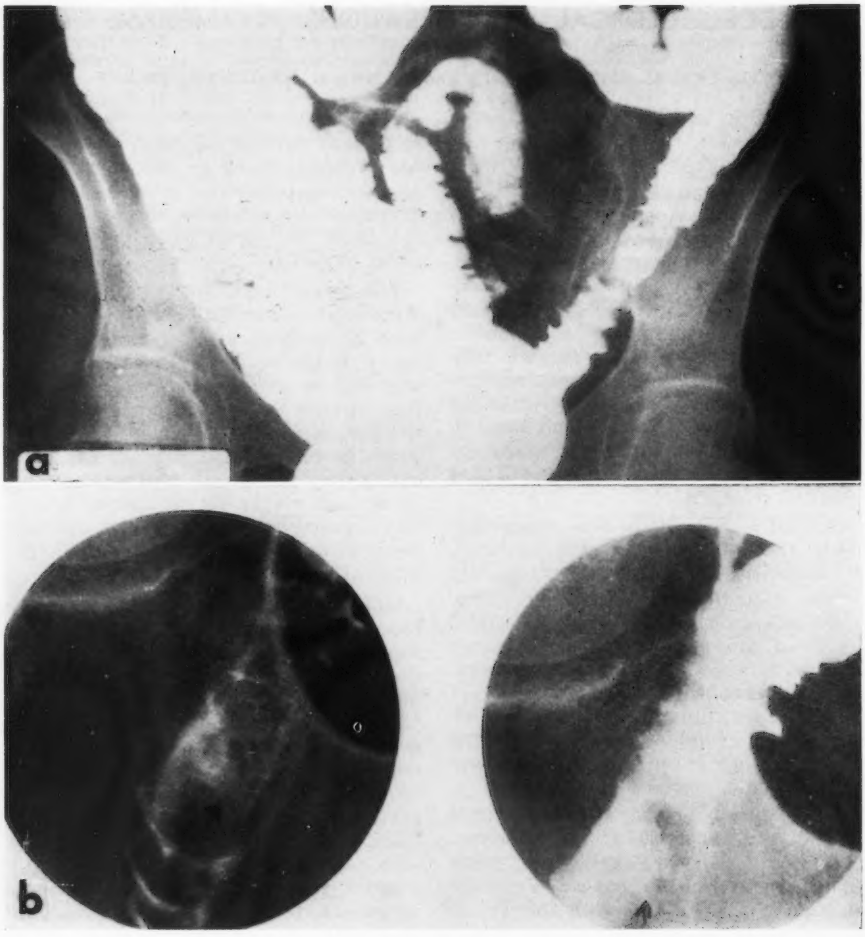

Figure 1.

a. Carcinoma of the descending colon (42 year old woman).

b. Spot films of (a)-arrow indicates ulceration in the carcinoma.

the clinician, this is the greatest problem in amebiasis. In which patients, if any, with "irritable colon syndrome," who have infections with large or small race *E. histolytica* is the predominating cause of their symptoms, the parasite, *E. histolytica?* There is no simple answer to this question. We have judged that when a patient is diagnosed parasitologically and responds to specific amebicidal therapy, when he has not responded to previous non-specific therapy, that patient probably was suffering from amebiasis. This diagnosis is rendered even more reliable in our minds if the patient later experiences a clinical relapse and again is found to have amebas in his stool and again responds to specific therapy. Unfortunately, we have been able to amass a great deal of supportive evidence of this nature. Our patients with small race *E. histolytica* have

frequent (50 to 60 percent) clinical and parasitologic relapses.

The similarities of the symptoms described above (bloating, selective dyspepsia to fried and fatty foods, etc.) to those enumerated for chronic gall bladder disease are striking. Indeed it is by no means a rarity to find patients with these complaints who have been subjected to cholecystectomy because these symptoms prompted an x-ray examination of the gall bladder which provided unequivocal evidence diagnostic of gall bladder disease. One would not question the wisdom of surgical intervention for proved gall bladder disease. However, in these cases the pathologic gall bladder was evidently not productive of the symptoms which led to the x-ray examination. Actually, the symptoms of bloat, gas, etc., particularly on eating specific foods usually depend on changes in the upper and lower gastro-intestinal tract and not upon the gall bladder. *E. histolytica,* it would appear, may produce such changes. Of interest is the fact that many patients whose symptoms are not relieved by the removal of the gall bladder, and evidently were not caused by it in the first place, are later classified as examples of the "post cholecystectomy syndrome."

The same patient with the chronic low grade complaints of bloat and gas and slight irregularity of bowel action may present himself with all the findings of amebiasis, proctoscopically and parasitologically and may in addition be found to have a filling defect in his colon on x-ray examination. Does this patient have a carcinoma or an ameboma? If the x-ray picture is clearly defined with a characteristic shelf-like picture, the patient probably has carcinoma of the colon complicated by amebiasis (Fig. 1 a & b). If he has a "ragged cecum," a trial therapy with emetine, carbarsone or atabrine may prove extremely worthwhile with subsequent disappearance of the lesion revealed by x-ray. Figure 2 (a & b) shows a typical ameboma. It should be pointed out that the patient with carcinoma of the colon may respond symptomatically to antiamebic therapy, lending credence to the complicating effect of the amebiasis, but being very misleading, clinically. Thus, x-ray follow-up is essential.

At the risk of belaboring the complications, it must be considered that an

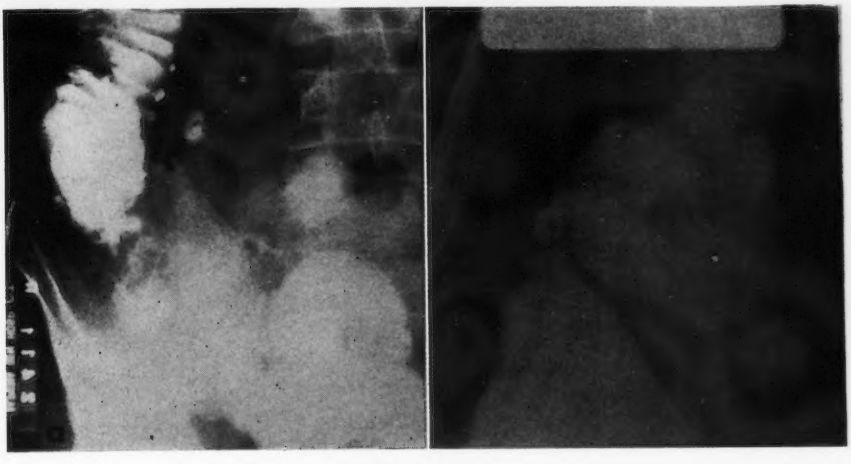

Figure 2.

a. Ameboma of the cecum in 52 year old man before therapy.

b. Cecum after therapy, showing only edema of the ileo cecal valve.

amebiasis or non-amebic unstable colon may effectively mask the pain—food—relief symptoms of peptic ulcer. The severe hunger spasm simulating peptic ulcer may on the other hand be part of the picture of amebiasis.

Another not uncommon finding is that a patient may be suffering from a malabsorptive syndrome either primary or secondary to an amebiasis and have a steatorrhea. The mild non-tropical sprue syndrome patient may even be so unfortunate as to excrete numerous *E. histolytica* in his stools, the treatment of which does little except to aggravate his symptoms. Another individual with the same complaint may, on thorough examination by x-ray of his large and small bowel, be diagnosesd by the radiologist as having "early rugal fold changes suggetive of regional ileitis." (Fig. 3 a & b). When such a patient has been shown to have amebiasis, the only guide we know to the diagnosis is the therapeutic trial with amebacides followed by re-x-ray. An extreme example is the case of a senior medical student whose findings on x-rays were typical of regional ileitis; at laparotomy, an ameboma of the caecum with a normal terminal ileum was found (Fig. 4). A somewhat easier clinical problem is a patient with amebiasis who had obstructive symptoms together with an x-ray demonstrated lesion either of the ileo-cecal valve or ileum. Laparatomy in this instance disclosed a carcinoid of the terminal ileum (Fig. 5).

Lastly, there is the patient who states that occasionally his diarrhea is accompanied by the passage of a few streaks of bloody mucus. In such an instance, the parasitologist may report the presence of pus, macrophages, RBC's, mucus and *E. histolytica* trophozoites, large and/or small race. On sigmoidoscopy the patient's rectal and sigmoidal mucosa is friable, purulent and contains a few scattered superficial ulcerations. He responds very well to the use of amebacides but 6 months later is back again with the same symptoms and findings including *E. histolytica.* On this occasion, however, specific amebacides produce no clinical benefit whatsoever. How shall we classify this patient? It is

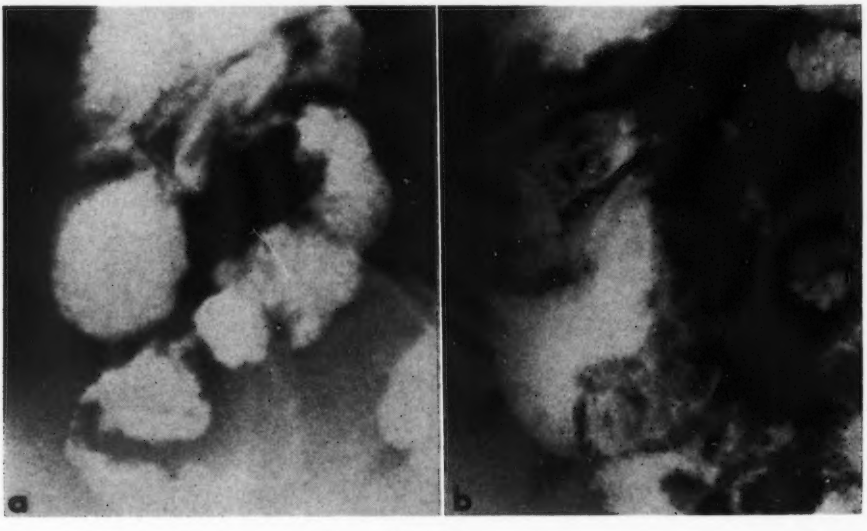

Figure 3.

a. Early rugal fold changes in the terminal ileum of a patient with amebiasis before therapy.

b. Terminal ileum of the same patient after therapy for amebiasis.

Figure 4.

Ameboma of the cecum simulating regional ileitis in 22 year old medical student. The diagnosis was made on a surgical specimen.

likely that this patient has non specific ulcerative colitis precipitated the first time by an amebic infection. It is our opinion that most patients with the proctoscopic picture of non specific ulcerative colitis are suffering from that disease, even though their stools may contain amebas and even though they may respond promptly to amebacides. There may be a future occasion when amebacides are not effective in producing a remission.

This unique parasite is also capable of migrating from the intestinal wall to the liver, lung, brain, and even pericardium. The particular circumstances which determine whether or not a given individual will suffer migration are still to be defined, although it is known that the malnourished and the alcoholic are more prone to the complication of hepatic amebiasis. Fig. 6 a & b illustrates typical x-ray findings in amebic liver abscess. Of 16 cases of proved hepatic amebiasis seen in the Chicago area by the authors in the past 10 years, only two have occurred in relatively well nourished people. The other fourteen patients have been seriously malnourished, ten of them being alcoholic. Many of this group of patients run low grade fever, have some anemia, and a mildly elevated white blood cell count. They tend to have moderate tenderness of the liver edge with some dullness to percussion at the right lung base posteriorly and diminished breath sounds. The chest x-ray findings are often interpreted as showing a pleural effusion of tuberculosis origin, and much time may be lost pursuing this diagnosis. In one such patient, the diagnosis was made by pleural puncture after the amebic abscess had ruptured into the pleural space. The pleural fluid contained many trophozoites of *E. histolytica* and culture was readily established. A right lateral chest film is usually of help in differentiating infra diaphragmatic abscess. It may not help in the event of an effusion due to an amebic abscess, since "sympathetic effusion" into the pleural space often occurs with other infra diaphragmatic pathology

Amebic liver abscess can be present without diarrhea and without amebas in the stool, but should always be suspected when chronic fever and hepatic tenderness exist together with no other signifi-

Figure 5.

Carcinoid of the terminal ileum in a 50 year old man with amebiasis.

cant diagnostic findings of other disease processes. Usually, finger-point tenderness over the liver is found to help point the way, but a high index of suspicion provides the only impetus. Caution is quite necessary. Actually, patients with all the diagnostic signs of amebic liver abscess have proven to be carbuncle of the kidney, empyema of the gall bladder and actinomycotic liver abscess, the latter diagnosis being made at post mortem.

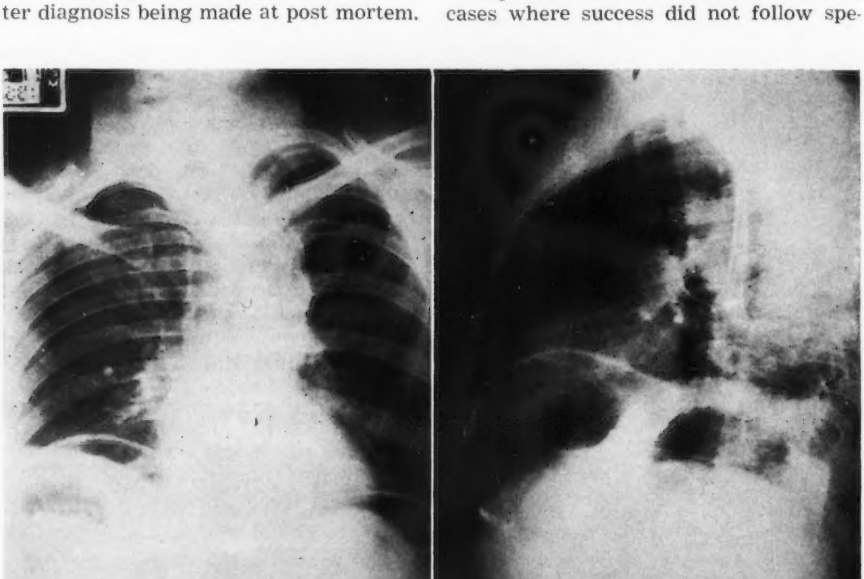

Figure 6.

a. Amebic liver abscess containing injected air, A—P view.

b. Lateral view of the same patient.

Discussion

The clinical problems outlined above serve to focus attention, perhaps, on the basic problem in amebiasis. This problem involves the significance of the parasite, *E. histolytica*, particularly the small race which is found so frequently in this area when adequate stool examination is performed. Actually, the best evidence for a role for the amebas lies in the results of therapeutic trials and this must always be considered as circumstantial. At least, in any individual case, the success of specific anti-amebic therapy must be viewed with caution and it is only after many such observations that such therapeutic success becomes of possible significance. The authors have studied well over 400 cases of the type described above in which a very high percent of therapeutic success occurred. In those cases where success did not follow specific anti-amebic therapy, there was, almost without exception, carcinoma of the colon, ulcerative colitis, mal-absorptive syndrome or other co-existing conditions. Such observations arouse a high degree of suspicion that *E. histolytica* is a contributor to the symptoms in many, if not all, of these individuals.

Perhaps much of the reason for so much varied clinical opinion about this subject lies in the fact that so much

study of the patient is required before, during and after therapy in order to assess the role of the parasite in an individual case. It cannot be too frequently emphasized that the mere finding of *E. hystolytica* does not establish the diagnosis, as illustrated by the instances where there is co-existing carcinoma, in which case the amebas are almost certainly of secondary importance. There are, obviously, other situations in which this is also the case. There are certainly many times when the diagnosis and treatment of amebic infection are lifesaving, as illustrated by the actual cure of liver abscess or by the possible prevention of its development by adequate therapy of a case of amebiasis. The dramatic results of the treatment of acute amebic dysentery should also be noted.

The role of *E. histolytica* obviously varies widely in different circumstances, and probably varies from time to time within the infected individual. The biological considerations involved here have been discussed more extensively elsewhere (Shaffer and Shlaes, 1958). It should be pointed out, in this connection, that although few cases of acute dysentery occur in temperate zones, some explosive outbreaks have occurred as illustrated by the Chicago World's Fair outbreak of 1933 and the more recent outbreak in South Bend, Indiana. One suspects that such outbreaks will continue to occur sporadically as long as *E. histolytica* is present in the human population.

Until more is known of the fundamental nature of the amebas, the relationships between small and large race *E. histolytica* and *E. hartmanni* and the complex interplay of biological forces in which they exist, the clinical aspects of amebiasis will remain complicated and confusing. Much also needs to be known of the epidemiology and immunology of these parasites. Solutions to the many problems will require much careful study and investigation.

SUMMARY

1. Numerous clinical problems presented by infection with *Entamoeba histoliytica* have been discussed.

2. The complexity of the situation presented by amebiasis has been pointed out.

3. The need for careful clinical and parasitologic evaluation of patients in attempting to evaluate what role *E. histolytica* may be playing in any given situation has been emphasized.

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TUMORS OF THE HEART

A Review of the Literature

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Historically, tumors of the heart have been of considerable interest since Zollicoperus wrote De Polyps Cordis in 1685[1]. The earliest reports of primary tumors are not clearly authenticated. Boneti in 1700 and Morgagni in 1762 may deserve this credit but it is accepted that Albers in 1835 reported the first authentic case of a primary fibroma and Bodenheimer in 1865 the first primary sarcoma[2]. In 1783 De Senac stated that "the heart is an organ too noble to be attacked by a primary tumor." Approximately fifty-two years later Billard in 1835 expressed the same thought in a more poetic vein when he wrote, "the heart is too sensitive an organ that it may continue to beat with a tumor within it. The tumor does not have time to develop."[3]

Despite a growing and extensive literature, primary tumors of the heart, while no longer rare, are certainly uncommon. Their incidence is becoming more manifest with improvement in diagnostic procedures and with greater clinical awareness of their presence. The over-all tabulation of all primary tumors, benign and malignant, is about 500 cases[4]. Statistics verify the fact that secondary or metastatic cardiac tumors are considerably more frequent than primary tumors. In a review of 8550 autopsies at the Mayo Clinic, Lymburner[5] in 1934 found 52 cases of metastatic and 4 primary tumors of the heart; none of the four were malignant. In 1945 Straus and Merliss[2] quoted statistics indicating a frequency of primary heart tumors of only 0.001% in 480,331 autopsies. In 1939 Scott and Garvin[6] found 118 metastatic heart tumors among 11,100 autopsies. Prichard[7] in 1951 compiled 8414 autopsies from six institutions and found 326 cases of metastatic cardiac lesions. In 1953 and 1954, study of 1264 patients dying of malignancy revealed cardiac lesions in 20% at autopsy[8, 9, 10].

Cardiac metastasis may occur by three possible routes: embolic, direct invasion and lymphatic spread. There are several primary sources that are implicated with great regularity, namely, cancer of the breast and lung[11, 12]. The heart and pericardium may be involved with lymphomas[13]. Cancer of the kidney, esophagus, testis, naso-oropharynx and pancreas may metastasize to the heart. Cancer of the stomach rarely does[11]. When such metastases do occur, there are differences of opinion as to which side of the heart is affected most frequently. Some reports favor the right, some the left and others quote an equal incidence on both sides[11, 14, 15]. Cardiac metastases usually appear as discrete nodules and all parts of the heart may be affected. There are no outstanding features that permit the identification of the primary site from the appearance of the cardiac metastasis with the possible exception of a pigmented metatasis of cancerous melanoma[15].

The heart does not differ from any other mass of striated muscle and connective tissue in the variety of primary tumors that may develop. The most common is the myxoma which comprises about 50% of all cardiac tumors. There is controversy as to whether these myxomas are organized thrombi or actual neoplasms, but regardless of this, the diagnostic and therapeutic problems are the same[16, 17].

In 1931 Yater[18] compiled 46 primary sarcomas of the heart; this was the first comprehensive review of the literature. During the next ten years, Weir and Jones[19] found 29 additional cases. In 1945 Mahaim[3] published his extensive monograph on tumors and polyps of the heart, including 87 cases of primary sarcoma to that date. By 1948 Whorton[20] was able to increase the number of primary sarcomas to 100, and in 1951 Prich-

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ard[7] added 13 cases. Cheng and Sutton[21] and Maronde[22] summarized the literature in 1955 and added 30 cases, including 10 of their own. Since then six more cases have been reported, making a total of 149 cases[4,23,24,25,26,27].

Primary sarcomas have a predilection for the right side of the heart. The cause for this is unknown. They occur in all age-groups and are equally present in both sexes[20,28,29]. Exact classification of these sarcomas is difficult because of variations in diagnostic and histologic criteria. Wharton[20] lists 20 pathologic-anatomic diagnoses in the 100 cases he reported. Histologically, most have been "spindle-cell" sarcomas of some sort, including fibrosarcoma, fibromyxosarcoma, myxosarcoma, leiomyosarcoma and rhabdomyosarcoma. Next in frequency are the "round-cell" sarcomas designated either by that term or as lymphosarcoma, reticulum-cell sarcoma or stem-cell sarcoma[25,26,30,31,32].

A not uncommon primary tumor is the rhabdomyoma. Two types have been reported. One is accepted as a true benign neoplasm and is classified as a fibromyoma resembling that found in the uterus because of its histologic structure[33]. The other is not considered neoplastic in nature. It shows a marked predilection for infants and is probably metabolic in origin, i.e., a localized form of von Gierke's disease. It is this latter lesion which is usually associated with other congenital anomalies and is found with cases of tuberous sclerosis, adenoma sebaceum of the skin and multiple tumors of the kidneys[11,34,35].

Other primary neoplasms include lipomas, fibromas, mesotheliomas, leiomyomas, teratomas, hemangiomas, dermoids and hamartomas[20,36,37,38,39,40,41,42,43]. No case of primary carcinoma has yet been reported.

The reason for the relative infrequency of primary tumors of the heart is unknown. It has been speculated that "the heart, above all organs, is constantly in a state of great efficiency, well nourished, well innervated and functionally always active, so that it is less likely to take on an aberrant growth".[44] It has also been explained by consideration of the relative size of the heart and its normal structure. The heart constitutes from 0.4 to 0.5% of body weight, while skeletal muscle from 40% of the total. Tumors of these organs might be expected to occur in numbers bearing the same relation as their weight. There is little if any mitotic activity in heart muscle and injuries result in degenerative rather than regenerative phenomena. The amount of connective tissue is small but probably shows more divisional activity than the muscle[45].

Prior to 1951 most cases of primary tumor of the heart were diagnosed postmortem and about 20 were suspected or diagnosed antemortem[7]. Since 1952, clinical diagnosis has been reported with increasing frequency and accuracy[22,23,46,47,48]. Reports of successful removal of these tumors, especially myxomas, are appearing in the literature[1,17,38,39,44,45,49,50]. Therefore, the nihilistic and discouraged attitudes expressed by earlier writers[3,7] can no longer be accepted as valid and the physician must of necessity become familiar with this condition.

The clinical diagnosis of cardiac tumors should be increasingly possible. All parts of the heart may be involved and all types of cardiac conditions may be simulated. Progressive, relentless cardiac failure, with no apparent or obvious cause, despite adequate treatment, as well as the presence of unexplained arrhythmias such as heart block, auricular fibrillation and flutter and nodal tachycardia is a characteristic feature of myocardial involvement. This has been stressed in the older literature as well as in recent reports[1,5,18,19,51,52,53,54,55,56].

Endocardial tumors or polypoid tumors projecting into the lumens of the heart may cause bizarre murmurs and intermittent or complete occlusion of the cardiac orifices. This is particularly true of the myxomas which are usually pedunculated. They are almost exclusively found in the atria, about 75% on the left side, and nearly always attach to or override the fossa ovalis or its rim[57]. Most of these produce some obstruction of the valve orifice. When the obstruction develops slowly, chronic congestive failure may result with dyspnea on ef-

fort, paroxysmal nocturnal dyspnea, fatigue, auricular fibrillation and peripheral emboli from necrosis of the tumor. If the obstruction occurs intermittently, as it often does, symptoms of a ball-valve occlusion may develop with episodes of Stokes-Adams syncope, epileptiform fits, symptoms suggestive of cerebral circulatory insufficiency and shock[52,57,58,59,60,61,62]. A left atrial tumor may produce a diastolic rumble and a systolic murmur at the apex, often associated with a loud, snapping first mitral sound, simulating mitral valve disease. However, characteristically, the murmur varies in intensity from time to time, may change in character with change in the patient's position or may be unusual in location. Increase in pulmonary pressure with accentuation of P2 may occur[16,17,63,64,65,66,67,68,69,70]. These intra-atrial tumors have a tendency to undergo necrosis. If fragments of the tumor break off, subacute bacterial endocarditis is simulated with intermittent fever, petecheae, changing murmurs and repeatedly sterile blood cultures[11].

Right atrial tumors, by partially occluding the tricuspid valve, may produce a tricuspid rumble that varies in intensity with change in position of the patient. In the absence of mitral and aortic valve disease, findings suggestive of tricuspid stenosis should arouse suspicion of an atrial tumor[34]. Sarcoma and other tumors on the right side of the heart may also cause superior vena cava obstruction with distension of neck veins, edema of the face, upper trunk and extremities and increased collateral circulation[71]. With all cardiac tumors precordial or chest pain is not uncommon.

Primary and metastatic cardiac tumors may involve the pericardium. The presence of acute pericarditis in a patient with known cancer should suggest cardiac metastases. Pericardial friction rubs and hemorrhagic effusions may result. Aspiration of such fluid and cytological examination may be of diagnostic value[4]. The clinical picture of constrictive pericarditis may be presented with increased venous pressure, hepatomegaly, ascites and edema. Unlike true constrictive pericarditis, however, ventricular pulsations may be normal fluoroscopically[18,72,73,74].

Electrocardiography is of limited value. It may help in the classification of arrhythmias, may show non-specific changes or RT segment modifications characteristic of pericarditis[4,12,36]. Roentgenographic studies showing unusual cardiac silhouettes and fixation of the heart with a rigid, hard, non-pulsating cardiac border may be of diagnostic value. Pneumopericardial studies following aspiration of an effusion may also help in outlining tumor masses[46,75]. More recently, diagnosis has been facilitated by angiocardiography[21,22,26,48,76]. McAfee, quoted by Harvey[16], cautions against this procedure because of the danger of intravascular thrombosis with a large concentrate of the dye introduced into the slowed and distended pulmonary circulation.

Summary: The antemortem diagnosis of tumor of the heart is desirable in view of the surgical progress being made in removing these tumors. While the diagnosis is still difficult to establish clinically, physicians must become aware of this possibility. The incidence of cardiac neoplasm is becoming more manifest and the diagnostic and therapeutic nihilism of the past is being dispelled.

While primary tumors of the heart are still relatively rare, they must be removed from the category of pathologic oddities. Antemortem diagnosis is being reported with increasing frequency and accuracy. Such diagnosis is made possible by a better understanding of the disturbed physiology of the heart and appreciation of the presenting clinical pictures, such as varying and changing murmurs, unexplained arrhythmias, valvular pathology in the absence of specific etiologic factors such as rheumatic heart involvement and progressive cardiac failure despite adequate treatment. Diagnosis is further facilitated by angiocardiography, cytological examination of pericardial fluid, roentgenographic and electrocardiographic studies. Finally, it may be categorically stated that a high index of suspicion in the presence of any unusual or bizarre cardiac condition may aid in directing the diagnosis towards a cardiac tumor.

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OSTEOARTHRITIS; DIAGNOSIS AND TREATMENT

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Definition: An effort to define osteoarthritis is an exacting and usually an unsatisfactory task inasmuch as the nature of this disease is so poorly understood and the limits of its clinical behavior are but dimly outlined. The term "osteoarthritis" has been used synonymously in this country with hypertrophic arthritis, also with degenerative, senescent, menopausal and traumatic arthritis and with osteoarthrosis. Perhaps the best one can do is to designate osteoarthritis as a non-inflammatory disease resulting in painful disorganization of joints without accompanying evidences of inflammation or infection.

Types of Osteoarthritis: Two great forms are encountered, these have been designated respectively, primary and secondary. The primary variety may be looked upon as a true diseased entity which is capable both of progression and extension, and having a distinctive evolutive pattern. Secondary osteoarthritis refers to the deterioration of a joint which may develop after severe trauma or in the wake of other destructive processes such as pyogenic infections. Secondary osteoarthritis is apt to be monoarticular. Primary osteoarthritis is an ailment encountered for the most part among patients beyond the age of fifty although exceptional instances appear prematurely and may affect individuals who are still in the late twenties or in the thirties. Secondary osteoarthritis may be encountered at any age and is dependent upon the occurrence of an earlier injury or infection.

Symptoms of Primary Osteoarthritis: Pain and stiffness of joints generally appear insidiously with this disease. When it is well established, the course is slowly progressive. Rarely, however, the onset may be abrupt, sometimes provoked by trauma or overexertion. In some instances, the onset occurs without recognizable provocation. When symptoms appear it may be taken for granted that primary osteoarthritis has been present in a quiescent phase for a long time. As evidence of this point, roentgenographic evidences of hypertrophic spur-formation and even deterioration of cartilages are often well advanced when symptoms are first noted.

The usual subject of primary osteoarthritis is an elderly and overweight individual, but the physician will do well to remember that osteoarthritis is by no means confined to this type. The thin and the underweight may also be affected. Aside from the articular disorder, the patient may show little evidence of any systemic ailment. A loss of weight is almost never attributable to osteoarthritis. Muscles adjacent to affected joints do not become atrophied as in rheumatoid arthritis. Fever and leukocytosis are not seen. Chemical constituents of the blood and sedimentation rates generally remain within normal limits. Whereas anemia is characteristically present in rheumatoid arthritis, anemia is not a feature of osteoarthritis and various immunological tests such as the sheep-cell agglutination show no deviations from the normal. Abnormalities of general health when present, and deviations from normal in laboratory findings should be explained on other grounds than the arthritis. In a word, patients with osteoarthritis feel well excepting for paintful joints. Primary osteoarthritis appears to be a constitutional disorder without systemic disturbances.

Comment on Pathology of Osteoarthritis: Gross and histologic changes of osteoarthritis are similar for both the primary and secondary varieties of osteoarthritis. The lesions consist of a mixture of changes involving cartilages, epiphyseal bones and the various soft tissues which constitute the articular capsules. Cartilages undergo a characteristic deterioration or atrophy in the course of which the surfaces become pitted or striated, the normal bluish-white color changing

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to a dull opaque lusterless white. Later atrophy may progress to a point where the cartilage is more or less eroded or ulcerated leaving underlying epiphyseal bone exposed. Finally, almost complete denudation of articular surfaces may result. The effect on bony parts is paradoxical. Whereas cartilages become atrophied and may finally disappear, bony parts actually proliferate, so that increased thickness of the subchondral bone (eburnation) and overgrowth of bone at articular margins (spurs) characterizes the roentgenographic picture of this disease. To some extent, the capsule may be frayed, and tendon sheaths become dry and adherent as the disease progresses.

The synovial membrane plays only a minor roles in the pathologic processes of osteoarthritis. In some instances synovial membranes remain unaltered and hardly an inflammatory cell can be found on microscopic examination. In others, a degree of fibrosis or scarring is recognizable in the subsynovial layers. Occacionally the villous processes may elongate and hypertrophy somewhat, but this occurs only to a minor degree in comparison with that encountered in association with rheumatoid arthritis. Cartilaginous metaplasia has been observed within hypertrophied villi. Occasionally such islands of cartilage become detached and thereafter are free in the joint space, constituting a "joint mouse" or loose-body. Various outcroppings or spurs at articular margins may have the effect of interposing obstructions to normal action. Therefore gritty or crepitant noises may be felt and heard when the joints are moved and in severe cases, affected articulations appear enlarged or gnarled. Articular swellings such as are found in patients with rheumatoid arthritis, are not regularly encountered in osteoarthritis except after unusual trauma, whereupon serous or bloody effusions may be present temporarily. Chronic effusions are not characteristic of osteoarthritis. In some instances, however, the proximal and distal rows of interphalangeal joints may be both enlarged and swollen and the resulting picture is often quite difficult to distinguish from rheumatoid arthritis.

A remarkable and distinctive localization characterizes the lesions of primary arthritis. Joints most frequently affected are the terminal joints of fingers (Heberden's nodes). The middle group of interphalangeal joints are also susceptible but are less often affected than terminal joints. Certain segments of the vertebral column, especially the 5th, 6th and 7th cervical, and the lumbar vertebrae are often involved while other vertebrae tend to escape. Knees, hips, acromio-clavicular joints, temporomandibular joints, joints of the instep, carpometacarpal joints of thumbs, and metatarsophalangeal joints of the great toes are susceptible. The localization of osteoarthritis is often symmetrical, and this finding also causes much difficulty in distinguishing primary osteoarthritis from rheumatoid arthritis.

Etiology and Pathogenesis: By custom, pathogenesis of osteoarthritis has been attributed to aging, and to wear, inasmuch as this disease so often affects elderly individuals. If, however, wear and tear are factors related to the pathogenesis then surely other factors must also play a role. Thus important contributing influence are thought to stem from inherited tendencies, and from repeated slight injuries. An inherited pattern has been determined clearly for the form of osteoarthritis which affects terminal interphalangeal joints (Heberdon's nodes) for which condition a single autosomal gene is involved. This is sex linked, dominant in females and recessive in males. This same pattern has not as yet been shown to hold for other varieties of osteoarthritis than Heberdon's nodes, but the familial trait is most likely involved in all instances.

A relationship of osteoarthritis to repeated injuries is often seen in the fact that severe osteoarthritis occurs commonly among coal miners, farmers, and persons engaged in other types of heavy labor. Other potential factors related to etiology of osteoarthritis which have been under study, include endocrine disorders, a defective nutritional balance and defective circulation. None of these has as yet been established as related to osteoarthritis and in short, the nature of osteoarthritis is not at all understood,

except for the suspicion of an inherited tendency.

Clinical features of Osteoarthritis: The onset as a rule is extremely slow, hence patients can almost never designate a date of onset. This slow, insidious course may be punctuated by more violent episodes of painful lumbago, sciatica, periarthritis of the shoulder, and torticollis. For the most part, pain of osteoarthritis is mild in degree, is aggravated by use and weight-bearing and is relieved by resting. Acroparesthesias are often noted when finger-joints are involved. Affected joints may appear enlarged, motions may be somewhat limited and ankylosis is almost never encountered. General health remains unaffected. Effusions are rare. The joints are not warm to the touch.

Comment on some Special Localizations of Osteoarthritis: (a) Osteoarthritis of the hip (malum coxae senilis) is perhaps the most frequently encountered serious manifestation of osteoarthritis. This condition comes to the attention of patients because of pain on walking and stair-climbing. Discomfort is noted either in the groin, along the outer aspect of the thigh or about the knee. There is a tendency to develop a limp, the thigh tends to become flexed, and either everted or slightly inverted. The patient often has difficulty in dressing because of inability to maneuver the extremity, as in crossing the legs. Pain may be referred to the knee or even to the ankle so that the diseased hip may be completely overlooked unless the physician is wary. Roentgenograms show destructive changes, namely, narrowed, irregular articular surfaces and sclerosis within thickened subchondral bone. Cyst-formation is not uncommon in the diseased femoral head. Various hypertrophic spurs appear on margins of the femoral head, and about the acetabulum. Hypertrophic changes may be present also on nearby boney prominences, including the femoral and ischial tuberosities, and about the symphysis pubis. The condition most often is unilateral but sometimes affects both hips. By the time attention is drawn to the presence of osteoarthritis of hips by onset of symptoms, the disease is almost invariably far-advanced. Thus, little is known concerning the manner and time of its onset. In occasional instances congenital malformations such as coxa plana or acquired deformities resulting from fracture or dislocation may lay the groundwork. In others no preexisting deformity or trauma can be identified and the disease appears to arise spontaneously.

Malum coxae senilis differs from most other manifestations of osteoarthritis in regard to the degree of resulting incapacity. Because the hip supports the weight of the trunk and thus plays a dominant role in ambulation, loss of function of this joint causes a very serious handicap. When the process is bilateral, the result is often complete invalidism.

(b) Osteoarthritis of hands (Heberden's Nodes). Perhaps the most characteristic and best known features of osteoarthritis are knobby ridges appearing at terminal interphalangeal joints of fingers. These appear insiduously in most patients but occasionally are ushered in with an abrupt, inflammatory swelling. The process may extend to involve all of the digits, and in severe instances, deviations and flexions of the terminal segments may result. Not infrequent a small cyst-like lesion intrudes into superficial layers of skin about a terminal joint. These may open spontaneously and discharge viscous or glairy fluid. Among persons showing advanced stages of Heberden's nodes on terminal joints of fingers, some develop similar enlargements of middle group of interphalangeal joints. The proximal row of metacarpophalangeal joints are almost never affected.

(c) Osteoarthritis of the spine. Some degree of hypertrophic spur formation may be found in almost every individual who reaches the age of fifty, and this condition becomes increasingly frequent with advancing age. As in the case of osteoarthritis in other joints, such lesions are not always accompanied by symptoms, and frequently may be present for many years, reaching an advanced state of development before causing discomfort.

Vertebrae most often affected are the lower cervical and lower lumbar segments. However, middle dorsal segments are also susceptible. In fact, far-advanced

cases are encountered in which nearly every vertebral body appears to be involved. Occasionaly only a few vertebrae show advanced changes, and other vertebrae are unaffected. In some individuals involvement of vertebrae appears to be unilateral, or much more severe on one side than on the other. Roentgenograms may show various alterations affecting intervertebral discs as well as the vertebral bodies, namely narrowing and occasionally even disappearance of the intervertebral space. And in such cases adjoining vertebral surfaces tend to be serrated or irregular with various bony excrescences.

Osteoarthritis of the spine is often associated with osteoporosis and with changes in structure secondary to the fragility of bones resulting from osteoporosis. Thus it is not uncommon to find osteoarthritis of the spine associated with compression fractures of translucent vertebrae resulting from osteoporosis. Varying degrees of painful stiffness are noted when this condition causes symptoms, and symptoms may be completely absent in some persons with well-established spinal osteoarthritis and rather severe among others who may show only minimal roentgenographic changes. In some instances pain may radiate along the course of root-segments leading to confusion with protruding discs, cord tumors, and with various neurological disorders. If the pain radiates to the anterior portion of the chest, angina pectoris may be suspected.

(d) Primary osteoarthritis of knees. This condition is never present alone, being invariably associated with other stigmata of osteoarthritis such as Heberden's nodes, spinal osteophytes and so forth. Some individuals, however, show far advanced osteoarthritic changes in knees with relatively little trouble elsewhere. Symptoms include grating or crepitus with motions. Pain is especially marked after prolonged periods of standing and is notably aggravated by walking up and especially down stairs. When the condition is well established the knee may be enlarged and complete extension may be impossible because of hypertrophic outcroppings which interfere with normal function. From time to time modest amounts of fluid may accumulate especially after unusual activities which require the patient to be on his feet a long time. The knees may appear bowed or severe "knock-knees" may be produced by alterations in the surfaces of the knee-joints.

Roentgenographic findings agree in general with the usual picture of osteoarthritis. The first change is often a narrowing of the articular space resulting from atrophy of cartilage. When the process is further advanced irregular sclerotic surfaces replace the usual smooth subchondral plate of bone, cysts may appear in epiphyseal regions of femur, patella or tibia, and various osteophytic excrescenses make an appearance.

Differential Diagnosis of Osteoarthritis: The main problem of differentiation in osteoarthritis is the resmblance to rheumatoid arthritis. Although osteoarthritis characteristically affects older persons, rheumatoid arthritis may also appear during later decades of life, consequently it is not possible to rely upon age to distinguish the two conditions. Basic differences between the two conditions should be kept in mind, especially the systemic phenomena of rheumatoid arthritis, loss of weight, anemia, various vasomotor disturbances, and characteristic complications such as nodules, uveitis, and muscular atrophy adjoining affected articulations in rheumatoid arthritis.

A distinction from gout rests primarily upon the characteristic clinical pattern of gout together with evidences of disturbed metabolism of uric acid.

Treatment: Treatment for primary osteoarthritis should be based upon a careful appraisal of the patient as an individual as well as on an estimation of the location and severity of the osteoarthritic lesions. Once joints have been damaged by this condition, restitution to normal is impossible because of a limited ability of articular structures to heal. Treatment should be directed towards amelioration of discomfort and to what extent may be possible, to preventing the forward progress of articular changes.

Inasmuch as no specific therapy has been evolved for osteoarthritis most thoughtful physicians suggest a program

of conservative measures fitted to the individual needs of each patient. Basic ingredients of this program should consist of rest, physical therapy, adjustment of diet, medications for alleviation of pain, and certain orthopedic procedures. For some aspects of osteoarthritis surgical measures may play a helpful role.

Rest: Osteoarthritis does not lead to ankyloses, hence forced motions accomplish no worthwhile result. On the contrary, pathologic lesions of this disease appear to originate in erosion of cartilages a condition which is aggravated or accelerated as a result of wear and tear. Therefore, rest, in a broad sense is beneficial and exercise is harmful. However, the prescription for rest should be individualized. For painful Heberden's nodes, avoidance of activities such as knitting, sewing, typing, and excessive practice of musical instruments, may provide worthwhile benefits. For osteoarthritis of the spine, avoidance of lifting, stooping, and carrying of heavy objects should be encouraged as a method of resting the spine. For osteoarthritis of the knees and hips, avoidance of walking and climbing of stairs should be a basic ingredient of the rest program, and at the same time, consideration should be given to the question of whether individual patients should be required to walk with crutches or a cane in order to further rest the affected joints. During especially painful episodes the patient should be placed at rest in bed for periods of several days to a few weeks in order to permit almost complete rest of the painful joints. Thus, no rule of thumb is available for planning the rest program for osteoarthritis. Rather, this aspect of the therapy should be designated by the thoughtful and experienced physician in a manner appropriate for each patient. Some patients, with osteoarthritis, as a result of misconceived notions regarding this disease or as a result of misguided counsel of well-intentioned friends, wiggle the joints incessantly or subject themselves to various forced exercise programs in order to prevent ankylosis. These exercises are potentially harmful and should be discontinued in favor of a prescribed program of rest.

Physical Therapy: Experiences of centuries have lent dignity to the employment of physical therapy for the treatment of osteoarthritis. Most patients with this condition derive comfort from physical measures, including various applications of heat and massages. Manipulations and forced motions of all types should be omitted for reasons stated above. For most patients with osteoarthritis, a program of physical therapy may be arranged in a manner permitting conduct of this part of the treatment at home. Thus, inexpensive heat-cradles, employing light bulbs as a source of heat, can be purchased in this country for modest sums. Warm baths, diathermy sono-therapy, applications of warm wax, packing in various heated collations such as muds and sacks of salt or hay, have enthusiastic advocates. All of these are capable of providing a degree of comfort when employed in association with other measures of a well-rounded program for osteoarthritis.

Dietary Measures: Thus far no distinctive chemical disorder has been associated with osteoarthritis and no dietary item has been incriminated as responsible. Accordingly, manipulations of diet do not appear to be worthwhile for these patients. For the overweight patient, caloric restrictions should be enforced.

Medicinal Measures: Almost every patient with osteoarthritis can make good use of simple medications in order to enhance his comfort. In the first place on this list of medicaments are salicylates. In the form of either aspirin, or sodium salicylate, given in plain or in coated tablets, these remedies provide a degree of relief from pain without notable risk. For most adults, three to six grams of salicylates can be tolerated daily without indigestion and without either tinnitus or deafness.

Employment of steroids as oral medications for osteoarthritis presents a considerable problem to the physician. For many patients with painful osteoarthritis, notable relief is achieved with either cortisone or other steroids. On the other hand, the basic lesions of osteoarthritis appear to be unaffected by these hormones. When these observations are tak-

en into account together with the fact that the general outlook for persons with this disease is good, the risks and difficulties associated with steroid therapy are not readily justifiable. The individual physician, however, may at times secure for this patient significant relief from symptoms by administration of steroid hormones in full doses, for a brief period, or small doses for a longer period, providing he can keep the patient under close supervision in order to control and prevent toxicities and side-effects.

Intra-articular injections of steroids: A recently developed measure of treatment for osteoarthritis is the intraarticular injection of either hydrocortisone or meticortelone acetate. These may be injected directly into the larger joints without notable risks. The results of this procedure are in general limited to partial and temporary relief of immediate symptoms. Basic programs for combatting the disease need to be worked out with each patient in addition to the procedure of intrarticular injection.

Surgical procedures: Exceptionally severe problems are encountered from time to time in the handling of patients with osteoarthritis. For some of these, surgical measures when carried out by skilled orthopedic surgeons may provide lasting benefits. Among the surgical measures which may be employed in this manner are operations for spinal fusion, patellectomy, various arthroplasties of the hip, excision of hypertrophic excrescences from knees, and excision of osteoarthritic bunions.

In every instance surgical treatment for osteoarthritis should be undertaken with an understanding that the surgical procedure involved cannot eradicate the disease and at best can be expected to correct some local mechanical problem resulting from the pathological overgrowths. This of itself, however, may be a help of considerable importance. For example, in some instances where massive bony exrescences affect the motion of hip joint, excision of spurs when carried out in association with properly performed arthroplasties may restore useful motion and permit a patient to resume a more normal way of life. Some instances of severe osteoarthritis of the knee may be associated with the presence of loose bodies which constitute a mechanical impediment to motions of the knee joint and may aggravate the pathologic lesions of osteoarthritis by acting as a foreign body. These may be removed at a time when the knee joint is opened for exploratory cleanup procedures. Considerable relief of pain may result. If the posterior aspect of the patella is badly eroded (chondromalacia) the patella may be removed. For patients with osteoarthritis affecting the first metatarsal phalangeal joint, massive marginal overgrowth may be responsible for severe pain experienced with walking and this symptom may be relieved by surgical excision of the entire articulation.

Comments regarding fluid effusions in osteoarthritis: Ordinarily effusions are not encountered among patients with osteoarthritis. Occasionally, however, and generally following some unusual trauma, a moderate effusion may appear in an osteoarthritic joint. Such fluids are generally clear and viscous containing relatively small numbers of leukocytes (500 to 1000 per cu. mm.). The protein content is relatively low, one to 3 grams per 100 cc. After a severe blow the osteoarthritic knee may fill with blood and this should be removed at once in order to prevent the possible development of chronic hemorrhagic or villonodular synovitis.

Comments regarding secondary osteoarthritis: Trauma sufficiently severe to damage articular surfaces may initiate scar formation. Subsequently, repeated use of such damaged joints may result in development of a localized form of osteoarthritis.

Long-continued use of a pneumatic hammer for drilling may provoke osteoarthritis in wrists, about the head of the radius and about the first carpometacarpal joint. Similar changes may appear also among the small joints of the wrist and shoulder.

Degenerative arthritis, constituting in effect a form of secondary osteoarthritis, may appear prematurely in policemen, soldiers, salesmen, cooks, waiters, fac-

tory workers, nurses, dentists and others whose occupations require long standing.

Joints which have been disorganized by pyogenic or other destructive infections often show severe osteoarthritis years after the infection has been overcome.

Osteoarthritis of the hip is often secondary in the sense that a preceding destructive ailment has laid the groundwork for the later-appearing degenerative changes. Causes of such secondary osteoarthritis may include coxa plana (Legg-Calve-Perthes' disease); slipped upper femoral epiphyses, septic arthritis, congenital dislocations, congenital aplasia of the acetabulum, congenital anomalies of the proximal portion of the femur, coxa vara resulting from either rickets or osteomalacia, Caisson disease, and tertiary Syphilis (Charcot's joints). In general, basic principles of treatment applying to these conditions are the same as those applicable to primary osteoarthritis.

SUMMARY AND CONCLUSIONS

Osteoarthritis, most numerous of all rheumatic diseases, is a major cause of disability among our aging population. The cause of osteoarthritis has thus far eluded the efforts of research; however, trauma and hereditary mechanisms unquestionably play a major role. The mechanism of inheritance for one type of osteoarthritis, Heberdon's nodes, appears to be firmly established as a single autosomal gene, which is dominant in women and recessive in men. Hereditary influences are suspected, but less well defined, for osteoarthritis of other sites, especially often in hip and spine.

It is estimated that nearly thirty million Americans suffer with osteoarthritis, and among these perhaps four to five million are notably disabled by it. After the age of 30 years, the degenerative changes of cartilage and to some extent the associated hypertrophy of osseous structures which make up the basic pathologic picture of osteoarthritis, become almost universal. In this respect, osteoarthritis is an ailment conditioned by age and precipitated or aggravated by trauma. Probably infectious diseases and some poorly defined metabolic disturbances are also at fault. The major goal of research in the field of musculo-skeletal diseases today is the discovery of the major cause of osteoarthritis. Once this will have been determined the whole subject of rheumatic diseases will take on a new character and millions of persons presently disabled will have a new hope for a better life.

THE INDEX FINGER AND THE URETHRAL CATHETER

DAVID PRESMAN, M.D.*

The advances in medicine during the past few decades have been largely due to the development of elaborate technical apparatus and a vast array of diagnostic laboratory procedures. The field of urology, together with other surgical specialties, has accumulated an awe-inspiring conglomeration of complicated instruments and gadgets guaranteed to penetrate every portion of the genito-urinary tract for either diagnostic or therapeutic purposes.

It would appear that the diagnosis and removal of any offending lesion or foreign body is a matter of choosing the correct shiny weapon and attacking resolutely through the proper aperture of the patient. Added to this, is the ever growing number of esoteric laboratory procedures which can establish a diagnosis without the necessity of the doctor ever seeing the patient. With all these technical aids, it seems that the modern urologist can solve any clinical problem with a minimum of thought and a maximum use of gadgets.

Unfortunately, this Utopian state of affairs is a delusion. The indiscriminate and forceful use of instruments, no matter how shiny and elaborate, can result in severe trauma to a degree that a new specialty has been created, iatrogenic medicine, i.e., disease produced by the physician. Moreover, the routine ordering of innumerable laboratory tests is of value in only the occasional patient with a rare disease since the common conditions can be diagnosed with much simpler procedures. There is no substitute for an intelligent evaluation of the individual patient and the judicious performance of indicated diagnostic procedures and simple laboratory tests. Instrumentation has not yet replaced cerebration in the proper practice of medicine.

The point to be emphasized is that most urological conditions can be diagnosed by means of uncomplicated, non-traumatic diagnostic and laboratory methods. Complex and expensive procedures should be performed only if simpler methods prove inadequate. It is needless, and may be hazardous, to submit every patient with urinary complaints to the complete armamentarium in the urologist's portfolio. Even in this era of mechanical contrivances, a common sense approach to the practice of medicine presupposes that the diagnosis of disease by the simplest methods available is best for the patient.

Two simple and very useful basic tools for urologic diagnosis and therapy are the **index finger** and the **urethral catheter.** Although over-shadowed in recent years by more glamorous equipment, they still provide a great deal of information as to the patient's ills and help alleviate many of his symptoms.

The index finger, when inserted in the rectum, reveals the status of the prostate gland much more accurately than any other instrument devised to date. By far the greatest number of cases of carcinoma of the prostate can still be diagnosed solely by the rectal examination. The occasional small, early or suspicious lesion must first be discovered by digital palpation before more complex diagnostic procedures are instituted. In actual clinical practice, when carcinoma of the prostate is symptomatic, the lesion can almost always be diagnosed by rectal examination. This applies whether the symptoms are due to bladder neck obstruction or metastases.

Not infrequently the patient with prostatic carcinoma seeks medical advice because of backache or pain in the hips secondary to metastatic involvement of the lumbo-sacral spine, pelvis or pelvic lymph nodes. The urinary symptoms may be insignificant. Before submitting the patient to various pulleys, ropes and weights, a rectal examination should be performed in order to rule out the possibility of prostatic carcinoma. Every male

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over the age of 50 with backache merits prostatic palpation with the index finger. It is surprising how many patients with prostatic carcinoma complain chiefly of backache and have a lesion which can be easily diagnosed by rectal examination. The use of the index finger to palpate the prostate is not the sole prerogative of the urologist, but belongs to and should be utilized by all of his medical colleagues including surgeons, internists and orthopedists.

Other conditions of the prostate may also be diagnosed by rectal examination. Varying degrees of enlargement due to benign hyperplasia are easily palpable as are the presence of prostatic calculi, acute prostatitis and chronic prostatitis.

Inflammation and engorgement of the seminal vesicles are often associated with chronic prostatitis and may be the main cause of the patient's symptoms. It is well to remember that prostatitis and seminal vesiculitis may cause pain and discomfort anywhere between the waist and the knees. Vague aches and discomfort in the lower abdomen, lower back, groins, testes, hips and thighs may be referred from the prostate or seminal vesicles which are the seat of low grade inflammation. The rectal examination not only reveals the site of pathology but, by judicious massage and stripping of these structures, the patient's symptoms will be alleviated.

The index finger is also invaluable when difficulty is encountered in passing an instrument such as a catheter, sound, cystoscope or resectoscope. The posterior urethra may be angulated or distorted by a stricture or an enlarged prostate so that an instrument cannot be inserted without resultant trauma and bleeding. With the index finger in the rectum, the posterior urethra can be straightened and the tip of the instrument guided into the bladder thus minimizing the creation of a false passage with marked bleeding. This simple maneuver will avoid much pain and bleeding in a squirming patient and should eliminate the spectacle of a distraught physician grimly determined to force an instrument past any and all obstructions.

It is well to point out that when a rectal examination is performed to evaluate the prostate gland, the examiner should always palpate for other pathology. The index finger should feel above the prostate and around the entire circumference of the rectum. In this way, a silent, early, carcinoma of the rectum may be and has been discovered. A mass in the pelvis can be felt through the rectal wall when it is not apparent by abdominal examination. Thrombosed hemorrhoids and rectal polyps are often palpable. Chronic urinary retention with a distended bladder may be overlooked because a suprapubic mass cannot be felt abdominally. The distended bladder can be identified by rectal examination if care is taken to palpate above the prostate. A relaxed anal sphincter may be the only apparent sign of neurological disease and can provide a clue for further neurological studies. In other words, although specialization is the order of the day, it behooves anyone who inserts an index finger into the rectum to do a **complete** rectal examination regardless of his specialty.

This brief summary of the usefulness of the index finger would be incomplete without some mention of its practical attributes as well. The index finger is always available to the physician wherever and whenever the patient is being examined. No need to wait for an unhurried nurse or clerk to fill out requisition slips or take a leisurely trip to central supply. The instrument is constantly at "hand" and requires only a rubber glove and lubricant. Moreover, it is always in working order, its parts function efficiently at all times and it never has to be returned to the manufacturer for repairs. Its use involves no extra expense to either the patient or doctor and it is guaranteed for the life of the owner. Indeed, what other instrument devised by man can compare in utility and convenience with this simple but unique appendage!

A fitting mate to the index finger is the urethral catheter. We refer to the standard, soft red rubber catheter known as the Coude′ or Tiemann. This has a slight angulation at one end, enabling it to traverse the male urethra easily and without trauma even in the presence of a

large prostate or a contracted bladder neck.

The commonest complaints in the male with genito-urinary disease are secondary to pathology in the urethra and region of the bladder neck. It is essential in all these patients to determine the presence or absence of chronic urinary retention, i.e., the volume of residual urine. Abdominal palpation and percussion is of dubious value since the bladder may be atonic or the abdomen obese. Also, the development of chronic retention is slow and insidious so that the patient may have no sensation of incompletely emptying his bladder. The passage of a catheter remains as the sole method of ascertaining the presence or absence of residual urine.

This important diagnostic procedure should be performed on every male patient with symptoms referable to the lower urinary tract. It may also reveal the presence of a urethral stricture which can be the primary cause of the symptoms. Thus, by a simple maneuver, one can determine two important clinical facts: the degree of chronic urinary retention and the presence of a urethral stricture.

In this connection, a word about the undiagnosed lower abdominal mass is in order. Occasionally, the general practioner, internist or surgeon is confronted with the problem of a silent tumor in the lower abdomen. After an exhausting series of enemas and cathartics followed by the usual battery of expensive gastro-intestinal x-rays, not to mention proctoscopy, the final diagnosis remains in doubt. Speculation ranges from a large cyst to any one of many rare conditions described only in the fine print of any standard textbook. Since the patient has minimal or absent urinary symptoms, the possibility of a chronically distended bladder is never considered. As a last resort, abdominal exploration is performed and a chagrined surgeon exposes the offending organ which rightfully belongs to the domain of the urologist. The simple procedure of passing a small catheter would have revealed the true nature of the mass and prevented embarrassment to the physician as well as a needless operation on the patient.

Notwithstanding the urologist's devotion to the catheter, his medical colleagues shudder at the double jeopardy of trauma and infection. These complications can easily be avoided if two precautions are observed, namely, a small calibre catheter (size 14 or 16 F) and the gentle but expeditious passage of said instrument. A bladder can be emptied just as well with a small catheter as with a large one. The male urethra is exteremly sensitive and, although elastic, will not tolerate the insult of forceful stretching without responding with bleeding and pain.

In addition, and most important, gentleness must be the password of anyone trespassing upon this urinary passage. Rough manipulation has no place in any field of medicine and invariably will be followed by unpleasant sequelae. Gentle passage of a small catheter with care and dispatch will result in minimal trauma and a rare infection. The important information to be gained from this procedure more than compensates for the very occasional complication that may ensue.

Another useful function of the urethral catheter is the management of urinary retention following abdominal operations. Temporary inability to void postoperatively in middle and older age males is a frequent experience. Most surgeons prefer to catheterize the patients intermittently after waiting many hours in the hope that spontaneous voiding will occur. This results in overdistention of the bladder producing an atonic condition which only aggravates the situation.

It is much wiser to insert a small Foley-bag catheter and leave it indwelling for several days to keep the bladder empty and at rest. The catheter is then removed after the patient is out of bed and ambulatory. This allows the bladder to regain its tone and the patient to recover from the initial trauma of the operation. If there is no significant bladder neck obstruction, normal voiding will almost invariably be the happy result. The indwelling catheter is tolerated very well by most patients and it is far less traumic than intermittent catheterization after repeated unsuccess-

ful agonizing efforts to urinate. This same program of management can be applied to the cardiac patient in urinary retention following an acute coronary occlusion.

The indwelling urethral catheter also plays an important role in the management of the neurogenic bladder whether it be due to trauma, neurological disease, general debility or unknown etiology. By changing the catheter at intervals of one to two weeks, infection san be kept at a minimum and nursing care simplified. Since medical rehabilitation of these patients is limited, their comfort becomes a primary consideration. The judicious use of the indwelling catheter provides a simple method whereby a serious problem can be handled very satisfactorily over a long period with a minimum of risk.

CONCLUSIONS

Lest any misunderstanding prevail, the foregoing remarks should not be construed as a diatribe against the many helpful advances of modern medicine. I am an ardent proponent of all the new techniques and procedures that have accounted, to a large degree, for the progress of medicine. However, in our enthusiasm for gadgets and elaborate instruments we should not overlook the importance of simple fundamental procedures which carry a minimum of risk while revealing much vital clinical information.

Being a urologist, the emphasis of this discussion has been placed upon two basic tools of this specialty; the index finger and the urethral catheter. Obviously one can enlarge on this theme by using examples referable to other specialties as well. The general idea applies to all of medicine and simply stated is "everything in its place and first things first."

STANDARDIZATION OF DIETS BY USE OF THE EXCHANGE SYSTEM

By BARBARA HASEK*

As early as 1942 an awareness of the need for standardizing the values of food composition in diabetic diets was noted. It was decided that inadequate diet therapy for the diabetic patient could be attributed to inconsistent methods of diet calculation, lack of patient understanding and individualization, and insufficient teaching methods. Patients were confronted with the problems of complicated and inconvenient measuring systems, varied diet instructions, and difficult and unfamiliar terminology. Institutions and physicians each were using their own preferred methods of calculation in planning the diabetic diet and other diets.

In 1947 a committee comprised of representatives of the American Diabetes Association, American Dietetic Association, and the United States Public Health Service commenced working on a method for the alleviation and solution of these problems. Their objectives were twofold: 1) to prepare a set of representative food values suitable for use in dietary calculations; and 2) to develop a simplified method for planning the diet by using lists of foods with similar food values.[1] A lack of uniformity in food composition plus the great variations in individual daily utilization of food were the two main problems with which the committee was confronted. It was concluded that the differences in bodily needs far exceeded the differences in food

Table I.

COMPOSITION OF FOOD GROUPS[3]

FOOD	Approx. Measure 1 exchange	WT. Gm.	C. Gm.	P. Gm.	F. Gm.	Calories
Milk	1 cup (standard)	240	12	8	10	170
Vegetables						
"A"	½ cup	100	less than 3 grams	—	—	—
"B"	½ cup	100	7	2	—	36
Fruit	exchange varies	exchange varies	10	—	—	40
Bread Exchanges	1 slice bread	25				
	Other items vary	varies	15	2	—	68
Meat Exchanges	1 oz. varies	30 varies	—	7	5	73
Fat Exchanges	1 level tsp. fat					
	Other items vary	5 varies	—	—	5	45

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composition. For this reason the problem of the inevitable variation in food composition was minimized.[1] Reasonable accuracy in calculation was sufficient. Hence, the foods were grouped as to similarity of composition.

Calculation of the Diet: The calculation of the diabetic diet is based upon the concept of the "food exchange". Similar foods are classified into six groups according to their composition .(Table I.) The foods included within each specific group, when taken in the designated quantity, are approximately equivalent in terms of carbohydrates, protein, and fat; hence, the term "exchange". For example, if one serving of bread is allowed in the diet; the patient may choose any one item from the list of bread exchanges provided he eats only the amount specified for one serving or exchange. Patients are instructed in terms of these exchanges.

Milk Exchanges: One milk exchange equals 12 grams of carbohydrate, 8 grams of protein, and 10 grams of fat. Several forms of milk are presently available for use such as powdered milk, evaporated milk, buttermilk, etc. Therefore, all types of milk are included in the exchange lists. To simplify the procedure a cup is used as the standard unit of measure. One cup or 240 grams of skimmed or non-fat milk contains the same amount of carbohydrate and protein as does the regular milk only the fat has been completely removed.

Vegetables Exchanges: The vegetables are divided into three groups according to their carbohydrate content. The "A" vegetables are considered negligible in carbohydrate content as they contain three grams or less carbohydrate per 100 gram portion. These vegetables need not be computed in the diet, provided not more than 200 grams (1 cup) are taken at one meal. The "B" vegetables (table III) are those vegetables whose carbohydrate content is somewhat higher, 7 grams of carbohydrate and 2 grams of protein per 100 gram portion. The remainder of the vegetables containing an even higher amount of carbohydrates are included in the list of bread exchanges. (Table V.)

Fruit Exchanges: The amount of carbohydrate varies greatly with the type of fruit. The fruit exchanges have been set up according to amounts equaling 10 grams of carbohydrate. (Table IV.) These fruits may be canned, cooked, or frozen without sugar, or fresh. Fruits have been listed in both standard household measures and natural measure. Those fruits particularly high in ascorbic acid have been noted.

Bread Exchanges: This list was designed to include not only bread and bread

Table II.

MILK EXCHANGES[3]

This list shows the different types of milk to use for one milk exchange. One exchange equals 12 grams carbohydrate, 8 grams protein, 10 grams fat.

Type of Milk	Amount to Use	
	Household	Metric
Whole milk (plain or homoginized)	1 cup	240 Gm.
Evaporated milk	½ cup	120 Gm.
Powdered whole milk	¼ cup	35 Gm.
Buttermilk	1 cup	240 Gm.

If skim or non-fat milk is used, the carbohydrate and protein remains the same; however, fat (2 exchanges) is omitted.

Skim milk	1 cup	240 Gm.
Powdered skim milk	¼ cup	35 Gm.

products but cereals, grains, high carbohydrate vegetables, and the "starch" foodstuffs such as spaghetti, macaroni, and noodles. All items within this list equal 15 grams of carbohydrate and 2 grams of protein when taken in the designated amount. Bread and bread products are listed in terms of commercial servings; for example, 1 slice of bread or 5 soda crackers; whereas cereals and vegetables are determined in household measures. The use of the enriched or whole grain cereals is encouraged.

Meat Exchanges: All items within the group known as meat exchanges equal approximately 7 grams of protein, 5 grams of fat, and negligible amounts of carbohydrate. (Table VI.) This group contains a wide variation in calories depending upon the method of cooking. However, this is minimized when the food is incorporated into the diet. Commercial measures and ounces have replaced the gram. All meats with the exception of bacon and sausage may be interchanged with such items as poultry, fish, eggs, peanut butter, and cheese.

Fat Exchanges: All items within this group are equal to 5 grams of fat per exchange (Table VII). However, this group is not restricted solely to the well-known fats, but includes bacon, sausage, cream cheese, olives, nuts, etc. Here again the commercial and household unit of measure is employed.

A group of foods known as "free foods" containing negligible amounts of carbohydrate, protein, and fat may be taken **ad lib** by the diabetic patient unless contraindicated by the physician. This includes tea, coffee, salt, spices, vinegar, sour pickles, unsweetened cranberries, rhubarb, lemon, clear broth, gelatin, rennet tablets, and saccharine.

Table III.

VEGETABLE EXCHANGES[3]

(1) "A" Vegetables — less than 3 grams carbohydrate per ½ cup or 100 gram portion.

- Asparagus
- Broccoli
- Brussels Sprouts
- Cabbage
- Cauliflower
- Celery
- Chicory
- Cucumbers
- Escarole
- Eggplant
- GREENS
  - Beet Greens
  - Chard
  - Dandelion
  - Kale
  - Mustard
  - Spinach
  - Turnip Greens
- Lettuce
- Mushrooms
- Okra
- Pepper
- Radishes
- Sauerkraut
- String Beans
- Young Summer Squash
- Tomatoes
- Watercress

(2) "B" Vegetables — 7 grams carbohydrate. 2 grams protein per ½ cup or 100 gram portion.

- Beets
- Carrots
- Onions
- Peas, green
- Pumpkin
- Rutabagas
- Squash, winter
- Turnips

As opposed to the "free foods," there is also a group of foods which should not be included in the basic diabetic diet and for which special permission should be obtained from the physician. These foods contain concentrated amounts of sugar, or are prepared in such a manner that an approximation of their caloric content is impossible. They include sugar, candy, chewing gum, jam, jelly, preserves,

Table IV.

FRUIT EXCHANGES[3]

This list shows the different amounts of fruits to use for one fruit exchange. Each exchange contains 10 grams of carbohydrate.

Types of Fruit	Amount to Use	
	Household	Metric
Apple (2" diameter)	1 small	80 Gm.
Applesauce	1/2 cup	100 Gm.
Apricots, fresh or canned	2 medium	100 Gm.
Apricots, dried	4 halves	20 Gm.
Banana	1/2 small	50 Gm.
Blackberries	1 cup	150 Gm.
Raspberries	1 cup	150 Gm.
*Strawberries	1 cup	150 Gm.
*Canteloupe (6" diameter)	1/4	200 Gm.
Cherries	10	75 Gm.
Dates	2	15 Gm.
Figs, fresh	2 large	50 Gm.
Figs, dried	1 small	15 Gm.
Grapefruit	1/2 small	125 Gm.
Grapes		
Tokay and Concord, red	12	75 Gm.
Seedless Thompson, white	22	75 Gm.
Honeydew Melon, 1 medium	1/8	150 Gm.
Mango	1/2 small	70 Gm.
*Orange	1 small	100 Gm.
Papaya	1/3 medium	100 Gm.
Peach, fresh or canned	1 medium	100 Gm.
Pear, fresh or canned	1 small	100 Gm.
Pineapple, fresh or canned	1/2 cup	80 Gm.
Plums, fresh or canned	2 medium	100 Gm.
Prunes, dried	2 medium	25 Gm.
Raisins	2 Tbs.	15 Gm.
*Tangerines	1 large	100 Gm.
Watermelon	1 cup	175 Gm.
Juices:		
Apple	1/2 cup	100 Gm.
Apricot	1/3 cup	80 Gm.
Grape	1/4 cup	60 Gm.
Grapefruit	1/2 cup	100 Gm.
Orange	1/2 cup	100 Gm.
Peach	1/3 cup	80 Gm.
Pear	1/3 cup	80 Gm.
Pineapple	1/3 cup	80 Gm.
Prune	1/4 cup	60 Gm.

* Those fruits high in ascorbic acid.

honey, syrup, molasses, rich combination dishes, all pastries, soft drinks, wine, beer, and other alcoholic beverages.

A review of the six exchange lists shows that it is not necessary for the diabetic patient to purchase "'special diabetic foods" in order to maintain an adequate diet. With the exception of "water-packed" fruit (fruit canned without sugar) special foods are not recommended. They are not only costly for the patient; but the majority, though reduced in calories do contain some calories; and should, therefore be calculated as a part of the daily intake.

It may be noted here that these exchanges, although initially designed to simplify the procedure of diet calculation and meal planning for the diabetic diet, have since proved useful in setting up low calorie diets or any diet in which a given number of calories, or given quantities of carbohydrate, protein, or fat are desired.

Also the patient with diabetes or a weight problem may have other medical complications in which case additional dietary adjustments may be needed. For example, he diabetic patient may need a sodium restriction or a bland diet. Rather than confuse the patient with two separate diet lists, the exchange list can be modified so as to meet the specific requirement. Foods in Table I contain

Table V.

BREAD EXCHANGES[3]

This list shows the different amounts of foods to use for one bread exchange. One exchange equals 15 grams carbohydrate and 2 grams protein.

Types of Bread Exchanges	Amount to Use	
	Household	Metric
Bread	1 slice	25 Gm.
Biscuit, Roll (2" diameter)	1	35 Gm.
Muffin (2" diameter)	1	35 Gm.
Cornbread (1½" cube)	1	100 Gm.
Cereals, cooked	1/2 cup	35 Gm.
Dry, flake & puff types	3/4 cup	100 Gm.
Rice, Grits, cooked	1/2 cup	20 Gm.
Spaghetti, Noodles, cooked	1/2 cup	100 Gm.
Macaroni, cooked	1/2 cup	100 Gm.
Crackers, graham (2½" sq.)	2	100 Gm.
Oyster (½ cup)	20	20 Gm.
Saltines (2" sq.)	5	20 Gm.
Soda (2½" sq.)	3	20 Gm.
Round, thin (1½")	6	20 Gm.
Flour	2-1/2 Tbs.	20 Gm.
Vegetables		20 Gm.
Beans & Peas, dried, cooked lima, navy, split pea, cowpeas, etc.)	1/2 cup	
Baked beans, no pork	1/4 cup	50 Gm.
Corn	1/3 cup	80 Gm.
Pop Corn	1 cup	20 Gm.
Parsnips	1/2 cup	125 Gm.
Potatoes, white	1 small	100 Gm.
Potatoes, white, mashed	1/2 cup	100 Gm.
Potatoes, sweet or Yams	1/4 cup	50 Gm.
Sponge Cake, plain (1½" cube)	1	25 Gm.
Ice Cream (omit 2 fat exchanges)	1/2 cup	70 Gm.

Table VI.

MEAT EXCHANGES[3]

This list shows the different amounts of foods to use for one meat exchange. One meat exchange equals 7 grams protein and 5 grams fat.

Types of Meat Exchanges	Amount to Use	
	Household	Metric
Meat & Poultry (medium fat) Beef, Lamb, Pork, Liver, Chicken, etc.)	1 ounce	30 Gm.
Cold Cuts (4½" x ⅛") (Salami, Minced Ham, Bologna, Liverwurst, Luncheon Loaf)	1 slice	45 Gm.
Frankfurter (8-9 per lb.)	1	50 Gm.
Egg	1	50 Gm.
Fish: Haddock, etc.	1 ounce	30 Gm.
Salmon, Tuna, Crab, Lobster	1/4 cup	30 Gm.
Shrimp, Clams, Oysters, etc.	5 small	45 Gm.
Sardines	3 medium	30 Gm.
Cheese, cheddar type	1 ounce	30 Gm.
Cottage	1/4 cup	45 Gm.
Peanut Butter	2 Tbs.	30 Gm.

the following amounts of sodium.[2]

1) One Milk Exchange, approximately 120 mg.
2) One Vegetable Exchange, approximately 9 mg., provided the vegetables are fresh, canned or cooked without salt. Since certain vegetables have a higher sodium content than others, they must be eliminated from the exchange list. These vegetables are, celery, greens, spinach, sauerkraut, and beets.
3) One Fruit Exchange, approximately 2 mg. All fruits are allowed. Raisins and dried figs have a higher sodium content than other fruits, and in diets where an extremely low sodium intake is desired these fruits should be omitted.
4) One Bread Exchange, approximately 5 mg. Commercial bread contains about 170 mg. per slice; therefore, it is sometimes necessary to use only commercial or home-made salt-free bread, depending on the amount of sodium allowed. The following bread exchanges are included on the low sodium diet: beans or peas (dried), corn (fresh), grits, lima beans (fresh), macaroni, matzoh, noodles, popcorn (unsalted), oatmeal, parsnips, potato, rice, puffed wheat, puffed rice, cream of wheat, farina, ralston, rice, shredded wheat, spaghetti, sweet potato, and wheatena. The commercial cereals must be the long cooking type.
5) One Meat Exchange, approximately 25 mg. per ounce. An egg contains 65 mg. of sodium. All varieties of meat are allowed except shellfish, brains, kidney, and heart. Omit all smoked, salt-cured, dried, canned, and kosher meats or fish. All cheeses except "low-sodium" cottage cheese are forbidden. "Low-sodium" tuna, salmon, and peanut butter are available and may be substituted for the regular types.
6) One Fat Exchange contains a negligible amount of sodium provided unsalted fats are used; sweet butter, vegetable oils, salt free salad dressings. Omit bacon, salt-pork, sausages, cream cheese, salted nuts, cream, and olives.[2]

In a similar manner the exchange lists may be modified in consistency to

suit the specifications of the ulcer, bland, low residue, or low fiber diet.

Application of the Exchange Lists: By using the list of exchanges and their carbohydrate, protein, and fat values the specific diet prescription is calculated (Table I). Nutritional adequacy is assured by the inclusion of the "basic protective foods" which are recommended for the normal adult or child. For example, each diet should contain, unless otherwise indicated by the physician, 1 pint of milk for an adult or 1 quart of milk for a child, 2 to 3 servings of fruit, 2 servings of a green or yellow vegetable, and sufficient amounts of meat, poultry, cheese, or eggs to meet the protein requirement of one gram per kilogram of body weight. In cases where the patient displays a definite dislike for one or more of these foods, or if for therapeutic reasons one must be omitted, the deficiency often may be corrected by additional amounts of food from another group. Thus, the nutritional adequacy of the diet is maintained. To calculate the diet proceed as follows:

1) Determine the amount of carbohydrate supplied by sources other than bread; e.g. milk, "B" vegetables, and fruits. Subtract this amount from the grams of carbohydrate permitted on the diet, and divide the result by 15; (the grams of carbohydrate in one bread exchange). This will give the number of bread exchanges necessary to complete the carbohydrate requirement.
2) In a like manner determine the grams of protein supplied from sources other than meat exchanges. Subtract this figure from the grams of protein allowed on the diet, and divide by 7; (the grams of protein in one meat exchange). The protein requirement is thus met.
3) Derive the number of fat exchanges by subtracting the grams of fat supplied by the milk and meat exchanges from the fat allowed on the diet, and divide by 5; (the number of grams of fat in one fat exchange). This will give the allowable fat exchanges.

Table VII.

FAT EXCHANGES[3]

This list shows the different foods to use for one fat exchange. One fat exchange equals five grams of fat.

Types of Fat Exchanges	Amount to Use	
	Household	Metric
Butter or Margarine	1 tsp.	5 Gm.
Bacon, crisp	1 slice	10 Gm.
Cream, light	2 Tbs.	30 Gm.
Cream, heavy	1 Tbs.	15 Gm.
Cream Cheese	1 Tbs.	15 Gm.
Avocado (4" diameter)	1/8	25 Gm.
French Dressing	1 Tbs.	15 Gm.
Mayonnaise	1 tsp.	5 Gm.
Oil or Cooking Fat	1 tsp.	5 Gm.
Nuts	6 small	10 Gm.
Olives	5 small	50 Gm.

The diet should be calculated as closely as possible to the specific diet prescription. However, it is not necessary to split exchanges for the sake of exactness. Use the number of exchanges that will provide the closest degree of accuracy. Carbohydrate may vary as much as 7 grams, protein as much as 4 grams. Fat amounts will always agree with theory since they are multiples of five. Reasonable proportions of carbohydrate to protein to fat are basic in a good diet prescription or it will be impossible to calculate the diet using this method and

Table VIII.

TOTAL DAY'S FOOD IN SAMPLE MEAL PLANS[4]

Meal Plan Number	Carbo-Hydrate Gm.	Pro-tein Gm.	Fat Gm.	Calories	Milk Exch.	Vegetable Exchange A	Vegetable Exchange B	Fruit Exch.	Bread Exch.	Meat Exch.	Fat Exch.
1	125	60	50	1200	1 pt.	as desired	1	3	4	5	1
2	150	70	70	1500	1 pt.	as desired	1	3	6	6	4
3	180	80	80	1800	1 pt.	as desired	1	3	8	7	5
4	220	90	100	2200	1 pt.	as desired	1	4	10	8	8
5*	180	80	80	1800	1 qt.	as desired	1	3	6	5	3
6*	250	100	130	2600	1 qt.	as desired	1	4	10	7	11
7*	370	140	165	3500	1 qt.	as desired	1	6	17	10	15
8	250	115	130	2600	1 pt.	as desired	1	4	12	10	12
9	300	120	145	3000	1 pt.	as desired	1	4	15	10	15

* These diets contain more milk and are suitable for children.

the diet will be unpalatable and difficult to prepare.

Division of the exchanges into individual meals will depend upon the patient's eating habits and the type of diet desired. If the patient is a diabetic, the carbohydrate should be divided as equally as possible to avoid a large amount at any one meal. Generally, if insulin is being administered, the total carbohydrate should be divided as follows: regular insulin, 1/3-1/3,-1/3; protamine zinc insulin, 2/7-2/7-2/7-1/7, the 1/7 representing a bedtime snack; NPH insulin, 2/7-2/7-1/7-2/7, the 1/7 being an afternoon snack.

The distribution of the carbohydrate compensates for variation in the action time of the different insulin preparations, and prevents excessive hunger at the time of maximal insulin action. For diets other than diabetic diets, the carbohydrate distribution is determined by the patient's eating habits. A good source of protein should be included in each meal if possible. Fat is distributed according to the patient's choice. In some instances the patient is given only the

Table IX[4]

SAMPLE MENU FOR A 1500 CALORIE DIET (Meal Plan No. 3)

Breakfast
- Fruit, 1 serving
- Egg, or other meat exchange
- Bread, 1 exchange
- Butter, 1 level teaspoon or other fat exchange
- Tea or coffee as desired

Lunch or supper
- Meat, 2 exchanges
- Bread, 2 exchanges
- "A" vegetable, as desired
- Fruit, 1 serving
- Milk, 1 cup
- Butter, 1 level teaspoon or other fat exchange
- Tea or coffee as desired

Dinner or main meal
- Meat, 3 exchanges
- Bread, 2 exchanges

"A" vegetable, as desired
Vegetable "B," 1 serving, ½ cup
- Fruit, 1 serving
- Butter, 1 level teaspoon or other fat exchange
- Tea or coffee as desired

Bedtime
- Milk, 1 cup
- Bread, 1 exchange
- Butter, 1 level teaspoon or other fat exchange

list of total exchanges allowed during the day and left to plan his own individual meals.

In addition to the exchange list the committee prepared sample meal plans with various caloric levels suitable for the adult and juvenile patient (Table VIII). The grams of carbohydrate, protein, and fat suggested at these caloric levels may be readily converted into nutritious and palatable meals (Table IX). These standard sample menus can be used for both the diabetic and weight reduction diet. However, one must be careful so as not to rely upon these menus alone. The diets should be reviewed with the patient by the physician or dietitian in order that the necessary individual adjustments are made to suit his food habits.

The acceptance of the exchange system in the United States has been almost unanimous. It has been incorporated into medical texts and books on diet therapy. Colleges and universities use this method in their instruction of medical students and students of home economics. Most hospitals, institutions, physicians, and dietitians use this procedure in calculating diets.

The advantages of this system are many. The uniformity has enabled physicians and dietitians to calculate and plan diets with greater facility and accuracy and has eliminated the necessity of having to learn new methods. Institutions and hospitals have also profited by this standardized time-saving system. It is easily taught to patients in understandable terms and is nutritionally sound.

Most important, it is individualized to the patient's medical needs and personal eating habits; it requires little effort on the part of the patient to prepare, and the wide variety of foods available promotes palatability and economy. Therefore, the patient is receiving a diet designed especially for him; thus, adherence to the diet is more certain.

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A NEW UNIVERSAL ENDOSCOPE

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It is rather fascinating to trace the development of those instruments which have been and are used in endo(cysto)-scopy of the organs of the lower G U tract. Therefore, before the new universal endoscope will be described, the individual steps in the construction of cystoscopes in the past shall be explained.

When, in 1879, Nitze together with Joseph Leiter, the Viennese manufacturer of surgical instruments, created their first cystoscope, they had good reasons to be very proud of having constructed an instrument which permitted the visualization of the interior of the bladder and to detect possible pathologic changes there. This cystoscope represents the first step in manufacturing optical instruments for the genito-urinary tract. However, after some time, Nitze and Leiter, as well as other surgeons became aware that suppurations within the bladder or, particularly, severe hemorrhage during the act of cysto(endo)scopy rendered the inspection of the bladder impossible, since the water with which the bladder is filled gets turbid within a short time. Their next endeavor, therefore, was to invent an instrument which would provide a view of the bladder and also permit irrigation of the organ, if required.

It appears that Brenner, in 1887, was the first to construct such an instrument by separating the sheath of the cystoscope from the telescope. The instrument could be introduced into the bladder, the telescope removed, and the bladder irrigated through the in-lying sheath. When the returning stream of water had become clear enough to permit visualization, the telescope was re-introduced and cystoscopy could be satisfactorily performed. Thus, the irrigating type of cystoscope represents the second step in the construction of these instruments.

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Nevertheless, the same genius, Brenner, was still not satisfied because he wished to introduce small catheters into the ureters in order to perform necessary manipulations at this level and, possibly, higher in the renal pelvis. Actual, his initial intention was merely to separate the urinary stream from either kidney, and this he soon achieved by inventing the first ureteral cystoscope. The Frenchman, Albarran, then constructed the little appliance that today is called the lid of the ureteral cystoscope, with the help of which one could move and manipulate the ureteral catheter in whatever way he wished.

With this, the path for the third step was opened. Urologists were no longer satisfied with merely looking into the bladder and washing it during the act, if required, but they wanted to perform **endoscopic surgery.** Within a short time they were able to introduce many types of sounds, dilators, tiny forceps for biopsies, electric coagulators and, eventually, even larger instruments into the bladder and ureters. Thus endoscopic surgery became possible.

Since the usual cystoscopes were not wide enough to permit the passage of a large telescope together with the introduction of such surgical appliances, two separate telescopes were constructed. One was for the general diagnostic survey of the bladder, the so-called observation telescope. When the diagnosis was made, another, smaller telescope, so-called operating telescope, was introduced together with the required instrument, and endoscopic surgery could be started.

All the instruments mentioned so far had either telescopes with a rectangular lens system which permitted the inspection of the bladder wall at an angle of 90 degrees, or straight forward looking telescopes. The latter, in the long run, were not versatile enough, for many reasons which cannot be discussed here. The best example of such a cystoscope, which permits any work in the bladder—

and it should be stressed in the **bladder alone**—is the American Brown-Buerger operating cystoscope which, in those days, was a tremendous step forward in the field of urology.

Meanwhile, urology as a specialty progressed and the interest of urologists became concentrated more and more on the bladder neck and the area distal to it, where the various pathologic changes, such as the enlarged prostate, the median bar, lesions of the verum montanum, and other conditions are found. It was, therefore, only natural to develop an instrument which would permit the orientation and detection of pathologic lesions in the male posterior urethra, that is, the segment between the bladder neck and the external sphincter of the bladder.

Such an instrument had already been prepared by several French urologists who used it routinely to inspect the female as well as the male urethra; this was advisable in times when gonorrheal and other venereal infections greatly changed these organs. In other words, cystoscopy, which means the inspection of the bladder, was extended to the inspection of the urethra. Therefore, this procedure has correctly been named urethroscopy or, in a wider sense, **endoscopy** of the urinary channel.

It is only possible to inspect the posterior urethra by filling and dilating it with a constant stream of water. After a period of trials and errors, a telescope was devised for endoscopy of the urethra which diverts the line of vision 15 degrees from the horizontal. McCarthy, among others, constructed such an endoscope which gave a satisfying view of the posterior urethra and of the interior of the bladder. However, even the simplest surgical manipulation in the bladder, such as the introduction of catheters into the ureters, which can so easily be performed with the rectangular telescope, is difficult to do with this type of optical instrument, the so-called foroblique telescope.

Nevertheless, McCarthy was entitled to call this excellent instrument **panendoscope** because it actually permits the inspection of the bladder and the urethra. However, manipulations within the bladder, as was already pointed out, are difficult to perform. McCarthy's panendoscope represented the fourth and last step in the development of endoscopes for the G U tract.

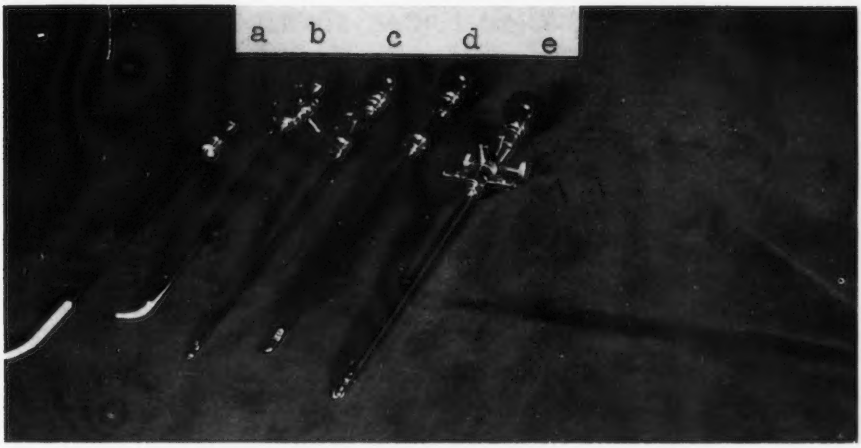
The new universal endoscope which was suggested by the author and manufactured by Englehard Industries, Inc., National Electric Division, is intended to make possible **any** inspection in the bladder and in the urethra of both sexes and, along with it, **any** surgical procedure in either cavity. The instrument, similar to the irrigating cystoscopes, consists first of a sheath which is introduced in the usual manner[1]. The circumference of these sheaths is rather small; either 16 French° (5 1/3 mm. actual size), or 20 French° (6 2/3 mm.). When the sheath has been introduced and the obturator removed, an observation telescope is first inserted to survey the bladder. After having noticed possible pathologic changes one may exchange the observation telescope for an operating telescope while the sheath remains in place. This telescope is simultaneously a double catheterizing and operating telescope so that any kind of cystoscopic operation can be performed in the bladder.

If no operation is required within the bladder, the operating telescope which, as mentioned above, has a rectangular lens system, can be removed and exchanged for the foroblique lens-system which permits not only posterior endoscopy but, since it has the necessary equipment, any surgical instrumentation in the posterior urethra[2] (manipulations of the ejaculatory and prostatic ducts; endoscopic operations on the verum montanum, and so forth), without again changing the position of the sheath.

With the sheath remaining unchanged in place no discomfort or harm is caused to the patient; with the help of three

1 Incidentally, even the sheath shows some features which are different from the others which permit a simpler and less dangerous introduction of the instrument into the bladder, especially if the anatomic conditions of the urinary channel make passage more difficult than usual, e.g., as in an enlarged prostate gland.

2 On addition, and if necessary, any examination of and endoscopic operation in the anterior urethra can be done, too.



a Obturator of instrument, flexible end
b Obturator inside sheath, flexible end
c Urethroscope (forward oblique telescope)
d Examining (observation) telescope, right angle
e Cystoscope with appliance for single and double catherism, right angle

kinds of telescopes and two different lens systems any lesion in the bladder and the urethra may be directly seen and treated. For the first time in the history of endoscopy, there is a universal endoscope which enables the urologist to perform all possible endoscopic examinations and operations in the genito-urinary tract by introducing the sheath of the instrument into the urinary ways only once, where it remains unchanged during the whole procedure.

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ESSAYS ON MEDICAL STATISTICS

ERNEST B. ZEISLER, M.D., Ph.D.*

I. INTRODUCTION

An increasing number of medical writings in the past twenty years have contained what purport to be statistical methods and conclusions ostensibly based on such methods. It has, consequently, been increasingly difficult for physicians and medical students to understand these writings and to know whether or not to accept their conclusions. In the words of Dingle:[2]

> The criterion for distinguishing sense from nonsense has to a large extent been lost: our minds are ready to tolerate any statement, no matter how ridiculous it obviously is, if only it comes from a man of repute and is accompanied by an array of mathematical symbols in Clarendon type.

For most readers it is impossible to distinguish "sense from nonsense" in much of modern medical literature.

There are essentially only four ways of obtaining conclusions. In two of these, *revelation* and *human authority*, the conclusion is obtained passively and entirely in reliance on some source outside oneself; in the other two, conclusions are obtained actively by the individual himself, either by *guessing* or by *reasoning*. Revelation is not within the domain of scientific discourse and will not be considered here. The acceptance of a conclusion in reliance on some human authority is based on the assumption that such an authority has obtained the conclusion either actively or from some anterior authority, and so on, so that we are ultimately relying on some authority who has obtained the conclusion actively, by himself. It is, therefore, necessary to consider only guessing and reasoning as the basis for conclusions.

No scientist can be willing to accept a conclusion based on guessing. Though such a conclusion may in fact be correct, especially if the guess was made by one very well-versed in the subject matter, yet it is not to be relied upon. We may be guided by what Sherlock Holmes said:

> It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts. (*A Scandal in Bohemia.*)
>
> I never guess. It is a shocking habit —destructive to the logical faculty. (*The Sign of the Four.*)

Bertrand Russell said:[7.2]

> I mean by intellectual integrity the habit of deciding vexed questions in accordance with the evidence, or of leaving them undecided when the evidence is inconclusive.

And again:[7.1]

> Truthfulness, as I mean it, is the habit of forming our opinions on the evidence, and holding them with that degree of conviction which the evidence warrants.

We will agree, then, that scientific opinion should be the result of reasoning from evidence, and is to be held only with the firmness which is warranted by the evidence.

Reasoning is inference in accordance with the laws of logic. There is only one kind of logic,[11] whether in mathematics, physics, biology, law, philosophy and so on. The tools used in reasoning may, however, vary with the subject-matter, one tool being more convenient for one purpose and another tool for another purpose. One tool which has often been found useful is *statistics;* when applied in biology this is called *biostatistics*, and when applied in medical science it is called *medical statistics.*

It is by no means necessary for the physician to be a statistician, and there

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is in general no reason for him to learn to use the tools of the statistician. But the physician should know in a general way what statistics can contribute to his knowledge and when he can gain by consulting the statistician. This is somewhat analogous to the relation between internist and neurosurgeon: the internist need not learn all the details of neuro-surgery, and need not be able to perform neuro-surgical procedures, but he should know in a general way what can be accomplished by neuro-surgery and when he should seek the aid of the neuro-surgeon. The physician who does not understand the general principles of statistics will be seriously handicapped in his study of much of contemporary medical literature, and will often not be able to decide what he should accept and what he should reject. One often meets with the attempt to support an opinion by an expression such as, "So-and-so has shown that such-and-such is true," when in fact so-and-so has *shown* nothing of the kind but has drawn his conclusions from inadequate evidence or by erroneous reasoning, and has merely *concluded* that such-and-such is true. Familiarity with the elementary principles of statistics will often suffice to avoid such errors on the part of a writer and their acceptance by a reader. (It should be evident that whether or not a conclusion is in fact true is beside the present point, which is whether or not a purported demonstration is valid.) Fortunately the necessary familiarity can be obtained by the average physician or medical student with no mathematical knowledge beyond very elementary high-school algebra.

II.

Every natural science can be divided into three parts: observation, the classification and organization of the evidence by observation, and inferences obtained by reasoning from the organized data. (One may add as a fourth part further observation designed to test the conclusions.) It is seen that a science is not a body of knowledge, but is a *method.* One particular science is the Science of Statistics, or the Theory of Statistics, or simply Statistics. In this particular science the three parts previously mentioned consist of 1) the collection of data, 2) the numerical organization of the data by classification and arrangement into *statistical tables,* which may be supplemented by representative diagrams, and 3) drawing conclusions by reasoning from the organized data. The first two of these involve no mathematics at all other than elementary arithmetic, but the third part is of necessity based on somewhat more complicated mathematical considerations.

The word "statistics" is often used to mean also either the unorganized or the organized data, but it seems preferable to reserve it for what we have called the Science of Statistics, and to refer to the the unorganized data as "raw data," and the organized data either as just that or as "statistical data." Confusion could also be avoided by following Levinson's suggestion of using "Statistics" to denote the Science of Statistics and "statistics" to denote the data.[4.1]

The popular and somewhat silly statestatement that "One can prove anything by statistics" rests on a grave misunderstanding. It is indeed the case that most absurd conclusions can be reached by the *misuse* of statistics, whether such misuse be the result of wilfulness or of incompetence, but such inference must not be called "proof." One could as well characterize surgery as butchery because some surgeons are butchers.

Essentially, then, the procedure in statistics is to obtain evidence and to draw conclusions from the evidence by valid reasoning. This is quite the same method as is employed in diagnosis, in which the evidence consists of symptoms and signs and the results of various tests and examinations by instruments of precision.

III.

A *universe* (or *population*) in statistics is a class (or aggregate) of things which are for some purpose considered together; the individual things in the class are its members, which may be of diverse kinds, such as persons, kernels of corn, kidneys, and what not. If every member of the universe has been examined, then the organized data constitutes a description of the entire universe, and

there is no place for statistical inference. In many practical problems, and in most biological problems it is impossible to examine every member of the universe, and one examines a *sample*, that is a *proper part* (a part less than the whole) of the universe. One then tries to draw conclusions about the unexamined part of the universe on the basis of what has been learned about the sample. Such conclusions are obtained by a form of *induction*.

We may immediately ask whether any sample will do, or whether particular kinds of sample are required. Yule and Kendall say:[10.1]

> The reliability of the data must always be examined before any attempt is made to base conclusions on them. This is true of all data, but particularly true of numerical data, which do not carry their quality writ large upon them. It is a waste of time to apply the refined theoretical methods of statistics to data which are suspect from the beginning.

Levinson says:[4.2]

> Reaching conclusions about an entire population from a sample is like enlarging a photograph. Small defects are magnified into serious blemishes.

The decision as to what data are needed for a statistical study depends on the kind of problem under investigation and on the general nature of the information one wishes to obtain. Hence the collection of data can be best planned only by one who understands both the problem under investigation and the requirements of statistical method. If it is not feasible for the planning to be done by such a person, then at least there must be collaboration between two persons, one of whom thoroughly understands the problem and the other of whom understands statistical method.

There is no general answer as to what constitutes an optimum or even an adequate sample, but some things can be said. In the first place, the sample must be large enough and varied enough to have represented in it all pertinent factors; and here there is already a difficulty, for one often does not and cannot at the outset know all the pertinent factors. In biological problems such factors may include age, sex, race, color, height, weight, geographical location, occupation, income, education, religion, and many other things. In the second place, the sample must be "fair," which means that every member of the universe must have the same chance of being contained in the sample as every other member; such a sample is called a *random sample*. We may say that all valid statistical inferences must be based on random samples.

It goes without saying that the choice of sample and the observation of its members must be honestly performed. But unfortunately this does not suffice. There must be *no possibility* that the choice of sample or its observation can in any way be influenced by the bias, conscious or unconscious, or by the judgment or lack of judgment of the sampler or of the observer or of anyone else, and this cannot be assured by honesty, good intentions, or training. Yule and Kendall say:[10.2]

> Experience has, in fact, shown that the human being is an extremely poor instrument for the the conduct of a random selection. Wherever there is any scope for personal choice or judgment on the part of the observer, bias is almost certain to creep in. Nor is this a quality which can be removed by conscious effort or training. Nearly every human being has, as part of his psychological make-up, a tendency away from true randomness in his choices.

And again:[10.3]

> . . . if we are to evolve a satisfactory method of random sampling we must eliminate all personal choice. The method of selection must, therefore, follow some code of procedure which leaves nothing to the observer's idiosyncracies.

Pearl expresses this as follows:[5.2]

> If personal judgment, skills, or what is fancied to be wisdom are

allowed to play any part in the choosing of individuals to go into the sample the result is practically certain to be biased. But if, on the contrary, some purely mechanical method of picking the individuals is rigorously and faithfully followed, without permitting judgments of what is good or wise to interfere with its operation, the sample is apt to be free of bias, provided the mechanical method was carefully planned in advance relative to randomicity.

And again:[5.3]

> In all statistical endeavor the idea ever to be striven for is to devise such mechanistic schemes or systems of sampling as will automatically exclude all necessity, and still more importantly, all opportunity for the exercise of judgment, fairness, or any other similar affective operation in the mind of the sampler.

Plausible devices such as the blind or even mechanical mixing of marbles or beads, or the shuffling of dice or of cards, have been found to be inadequate to assure random sampling. And it must be noted that the appearance of randomness is quite unreliable, for *it is theoretically totally impossible to prove that a given set of things is random;* the most that can properly be said is that no lack of randomness has been discovered.

IV.

The principles of statistical inference can not be grasped unless one knows the meaning of such terms as *frequency, frequency distribution, association, dissociation,* and *probability.* The necessity of *controls* in all observation and experiment can be thorough appreciated only by a study of the simple four-fold table of frequencies. One must understand such terms as *Gaussian* (or *normal*) *probability curve, mean, median, deviation, standard deviation, standard error* (*probable error*), *expected value,* and *correlation.* But it is necessary only to know the *meaning* of these terms, and is not at all necessary to be able to carry out the calculations entailed in their use. Mathematical training, while clearly not disadvantageous, is not a prerequisite for a sufficient understanding of statistics to serve the physician's purpose.

It is clear that no statistical inference from a sample to the whole could be possible without some assumption as to the nature of the universe which has been sampled. A common assumption is that the universe conforms to the Gaussian frequency distribution, but other assumptions are made at other times. Inasmuch as there can be no certainty at the outset that such assumption is in fact correct, there is of necessity some uncertainty about the truth of the conclusions. In addition, even if one waives any uncertainty about the assumption as to frequency distribution of the universe, the fact remains that no conclusion drawn from a sample can be *certain* as to the unexamined part of the universe, and that *all statistical inferences must be expressed in terms of probabilities.*

In recent years a great deal of medico-statistical reasoning has been based on the Chi-square test; and relatively recently some authors[1, 8] have attempted to apply Sequential Analysis[9] to medical statistics. The true value of these tests can be assessed only in the light of what is known as *Bayes' Rule* of *a posteriori* probability, which is not even mentioned in even the best books on medical statistics.[3, 5.1]

It may be mentioned, in closing, that *statistics alone can never under any circumstances demonstrate any kind of causal connection;* such demonstration, when it is at all possible, always requires non-statistical consideration in addition to the statistical.

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